EXERCISE TESTING IN HEALTHY HAEMODIALYSIS PATIENTS

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ABBREVIATIONS

H.R. - Heart rate (beats/min)

SBP - Systolic blood pressure (mm Hg)

DBP - Diastolic blood pressure (mm Hg)

H.R. SBP x 10^{-2} - Heart rate Systolic blood pressure product (arbitrary units)

M.A.P. - Mean arterial pressure (mm Hg)

T.P.R. - Total peripheral resistance (arbitrary units)

C.O. - Cardiac output (l/min)

C.I. - Cardiac index (l/min/m^2)

S.V. - Stroke volume (ml/min)

S.I. - Stroke index (ml/min/m^2)

Hb - Haemoglobin (gms/100 ml)

A_o - Arterial oxygen content (Vols %)

V_o - Venous oxygen content (Vols %)

$A\text{-}V_o\Delta$ - Arteriovenous oxygen difference (Vols %)

pO_2 - Arterial oxygen tension (mm Hg)

pCO_2 - Arterial carbon dioxide tension (mm Hg)

$\dot{V}_{O_2}$ - Oxygen consumption (ml or l/min)

$\dot{V}_{O_2}I$ - Oxygen consumption index (ml or l/min/m^2)

$\dot{V}_{O_2}Max$ - Maximal oxygen consumption (ml or l/min)

Pred. $\dot{V}_{O_2}Max$ - Predicted maximal oxygen consumption (ml or l/min)

H.R. $\dot{V}_{O_2}$ 0.75, 1.0, 1.5 - Heart rate at an oxygen consumption of 0.75, 1.0 or 1.5 l/min

$\dot{V}_{CO_2}$ - Carbon dioxide production (ml or l/min)

RQ - Respiratory quotient = $\frac{\dot{V}_{O_2}}{\dot{V}_{CO_2}}$

$\dot{V}_E$ - Minute ventilation (l/min)

$\dot{V}_E$ 0.75, 1.0, 1.5 - Minute ventilation at an oxygen consumption of 0.75, 1.0 or 1.5 l/min

R-R - Respiratory rate (breaths/min)

V_T - Tidal volume (ml or l/min)

FEV_1 - Forced expiratory volume in 1 minute (l)

FVC - Forced vital capacity (l)

$\frac{FEV_1}{FVC}$ - The ratio of FEV_1 to FVC as a percentage

P.D.S. - Physiological dead space (ml)

V_D/V_T - Ratio of dead space to tidal volume as a percentage

$A\text{-}a_o$ - Alveolar-arterial oxygen gradient (mm Hg)

ABSTRACT

1. Little work has been done on the response of regular haemodialysis patients to dynamic exercise. A systematic study of exercise capacity and the underlying mechanisms is of particular importance because these patients are encouraged to return to as normal a way of life as possible. Accordingly, a select group of healthy young male patients and a group of older males have been studied during submaximal cycling. The young male patients were compared to a closely matched sedentary control group. The 17 subjects discussed represent the fittest of 40 patients tested.

2. In both groups there was decreased work capacity associated with disproportionate tachycardia, which was not obvious at rest. Blood pressure was measured with a sphygmomanometer. During exercise there was a striking rise in the systolic blood pressure in about half the patients from currently acceptable resting levels. This occurred in the absence of any clinical circulatory overload. Mild hyperventilation and disproportionate lactic acidosis was seen towards peak exercise, probably because, in spite of the decreased work capacity, the patients were much closer to their maximum performance. However, the limiting factors were clearly circulatory and not respiratory.

3. A number of the younger male patients were more intensively studied to determine why some remained relatively 'normotensive' during exercise while others developed systolic hypertension. Total blood volume, total body water and plasma renin activity were measured at rest. It was found that the 'normotensive' patients had normal body volumes and normal to high plasma renin activity, while the hypertensive subgroup had increased volumes and normal to low plasma renin activity. Thus in these patients

the blood pressure responses to exercise were largely volume dependent, albeit at a subclinical level.

4. Cardiac output was measured at rest and during exercise. All patients developed a variable hyperkinetic circulation during exercise which was not apparent at rest. The patients were all anaemic and their cardiac output response was very like that described in patients with anaemia unassociated with renal disease. However, some patients with striking anaemia developed a less hyperkinetic circulation than others who were not so anaemic. When the body volume and the blood pressure response on exercise were considered, those patients who were normovolaemic and 'normotensive' developed a hyperkinetic circulation on exercise appropriate to their degree of anaemia. Those with subclinical volume overload and a hypertensive response to exercise developed a much less striking hyperkinetic circulation, suggesting that the blood pressure and volume excess was depressing the anticipated cardiac output response to their underlying anaemia.

5. One patient with an arteriovenous shunt was studied twice, initially when hypervolaemic with a haemoglobin of 9,1 gm/100 ml and again after ultrafiltration when he was normovolaemic but his haemoglobin had risen to 12,5 gm/100 ml. On the first occasion his cardiac output response was moderately hyperkinetic but he developed increasing hypertension with a high calculated total peripheral resistance. On the second occasion his cardiac output response fell within the normal range, his blood pressure was lower but not normal and his calculated total peripheral resistance was even higher than before. Thus the blood pressure of these volume dependent patients is due to a high total peripheral resistance, but may not simply be on the basis of 'waterlogging' of the peripheral vasculature. Some

other factor, such as structural thickening, must be considered.

6. It is suggested that the combination of tachycardia and hypertension which develop on mild exertion and which may not be obvious at rest, is the most potent cause of the increased cardiovascular mortality seen in dialysis patients. Simple exercise testing will reveal those with subclinical volume overload who are most at risk. It was striking that in the two groups tested those who developed striking hypertension on exercise were usually older, between 35 and 50 years. This accelerated aging of their vascular tree would correspond with recent data showing that dialysis mortality increases with age, and is about a decade earlier than in the general population. It is suggested that a more aggressive policy be adopted towards blood pressure fluctuations and that the resting blood pressure should be kept below 140/90 mm Hg at all times, if necessary by complementing ultrafiltration with drug therapy and/or bilateral nephrectomy at an early stage.

7. Thus simple exercise testing with blood pressure recordings not only serves as a yardstick of physical rehabilitation and long-term follow-up, but may also reveal or magnify abnormalities not obvious at rest.

CHAPTER 1

BACKGROUND TO BLOOD PRESSURE CONTROL AND HAEMODYNAMICS IN REGULAR HAEMODIALYSIS PATIENTS

1.1 Introduction

Data presented by Dr. F. Parsons at the European Dialysis and Transplant Association (E.D.T.A.) meeting in August, 1975, showed that in Europe on 31.12.74 there were 17,766 patients alive on haemodialysis and 4,213 patients with a functioning graft. Additional data showed that, apart from patients receiving a graft from a related living donor, transplantation has not to date proved to be the solution to patients presenting with end-stage renal failure, and that the long-term burden is falling more and more heavily on haemodialysis, both in hospital centres and in the patients' homes. This reliance on haemodialysis is presenting an increasing medical and socio-economic problem. The socio-economic problems are obvious, but the medical problems of regular haemodialysis are also escalating since it has become clear that there is an increased mortality from cardiovascular diseases and this appears to be the limiting factor to prolonged patient survival. This increase in cardiovascular related deaths is not a universal finding, but in the overall E.D.T.A. figures for 1974 it was responsible for about 60 per cent of the deaths occurring in the first six months on dialysis. It is now also evident (E.D.T.A., 1975) that patient survival is clearly age related and that whereas 75 per cent of patients aged 15 to 34 years survive three years on hospital dialysis, only 55 per cent of patients aged 55 to 64 years survive for the same period. Linder et al. (1974) have emphasized the appearance of accelerated atherosclerosis and showed that in Seattle the incidence of myocardia infarction, strokes and refractory congestive heart failure in their

regular dialysis patients was many times higher than in normal and hypertensive groups of comparable age and was similar to that found in Type 2 hyperlipoproteinaemia. This alarming problem has been commented upon editorially in a number of journals (Lancet, 1974; New England Journal of Medicine, 1974; and the Annals of Internal Medicine, 1974) and, although present research seems to be focusing more on the metabolic problems of hyperlipoproteinaemia, carbohydrate intolerance and metastatic calcification, it is generally accepted that uncontrolled hypertension plays a major role. The subject has recently been reviewed by Lazarus et al.(1975).

Hypertension is common in patients accepted for regular haemodialysis. Brown et al.(1971) found an incidence of 84,7% among 203 patients reported by several workers. During a 10-year period del Greco et al. (1975) found an initial incidence of 88,6% among 131 patients accepted for dialysis. In Johannesburg (Milne et al., 1974) 81 per cent of a group of 158 patients starting haemodialysis were hypertensive to some degree. Once on dialysis del Greco found that 11,4% of patients remained normotensive, 17,6% became normotensive, 62,6% had their hypertension controlled (but he does not specify at what level) and only 8,4% had uncontrollable hypertension. In the Johannesburg group 57 per cent had their blood pressure controlled below $\frac{140}{90}$ mm Hg, but 28 per cent continued with mild hypertension and 14 per cent with moderate hypertension. Thus, although the hypertension can be controlled in the majority of cases by haemodialysis, an appreciable number remain hypertensive.

1.2 Blood pressure regulation in regular haemodialysis patients

There have been numerous articles on the regulation of blood

pressure in these patients but only a few review articles will be mentioned (Lazarus et al., 1975; Hampers et al., 1973; Ledingham, 1971; Brown et al., 1971; Vertes et al., 1969). There is general agreement that hypertension is maintained by a high peripheral resistance, but precisely how this is initiated is poorly understood. It is also accepted that there are two main factors responsible for the maintenance of the high peripheral resistance and hence hypertension:

1.2.1 Volume dependent hypertension

Circulatory volume overload clearly plays the dominant role and is the most obvious factor in the vast majority of haemodialysis patients. This mechanism is seen most clearly in anephric patients (Berman et al., 1972; Coleman et al., 1970) where the role of the renin-angiotensin system is either negligible or largely unimportant. In the anephric patient the relationship between extracellular volume and blood pressure is largely predictable, but in those who have not been subjected to bilateral nephrectomy there is no clear agreement on which particular fluid or electrolyte compartment correlates best with blood pressure. The haemodynamic disturbances leading to hypertension are equally unclear. Following on the work of Borst (Borst and Borst-de Geus, 1963) who suggested that increased blood flow, i.e. a high cardiac output, may induce a high peripheral resistance by vasoconstriction, Coleman et al. (1970) gradually allowed the circulatory volume of three anephric subjects to increase and showed that there was an initial elevation of cardiac output with increased blood pressure but that the increased blood pressure was then maintained by a high calculated total peripheral resistance, while the cardiac output returned to normal. Ledingham and Pelling (1967)

showed the same sequence of events in partially nephrectomised dogs. This work has given rise to the so-called functional theory of autoregulation. There is much debate about the validity of this concept, and there is some work (Kim et al., 1974) contradicting the findings of Coleman et al. (1970) in dialysis patients.

1.2.2 Renin dependent hypertension

There is also a small group of haemodialysis patients, about five per cent of the total, whose blood pressure is largely uncontrollable by conventional ultrafiltration and drug therapy and whose hypertension can only be controlled by bilateral nephrectomy. These patients have been shown to have extremely high levels of plasma renin, angiotensin I and angiotensin II. However, the blood pressure response to bilateral nephrectomy is variable : in some the blood pressure falls dramatically, but in others (Hampers et al., 1967) there is a gradual return over some months to normal levels with sustained high levels of total peripheral resistance, suggesting some structural alteration of the peripheral vessels which takes time to resolve.

Finally there is probably a third group whose hypertension is sustained by an abnormal relation between volume overload and the renin-angiotensin system (Davies et al., 1973). In normal subjects exchangeable sodium correlates inversely with angiotensin I and angiotensin II levels. Unusually high levels of these hormones have been found in some hypertensive dialysis patients relative to their total exchangeable sodium suggesting that the renin-angiotensin system and volume overload may both be responsible for the hypertension.

1.3 Further haemodynamic studies

The initial method of access to the patient's circulation for haemodialysis was the arteriovenous shunt. This made possible numerous studies on the interrelationship of cardiac output, mean arterial pressure and calculated peripheral resistance using indicator-dilution methods. Kim, Onesti and Swartz probably have the widest experience in this area. Their latest review (Kim et al., 1975) compares the haemodynamics of 52 hypertensive patients, 23 normotensive patients and 42 normal subjects. The overall dialysis group, tested at rest in the supine position, had a significantly higher cardiac output than the normals, but there was no difference between the cardiac output of the hypertensives and the normotensive patients although the former had a higher peripheral resistance. A problem of performing cardiac output studies at rest only is that there is a wide scatter of results and a considerable overlap between those groups with high and those with a normal or low cardiac output. Nonetheless, a relationship has been found between volume overload, hypertension and a low cardiac output, while those with marked anaemia have a high cardiac output.

It is uncertain whether these cardiac output findings are related only to the degree of volume overload and hypertension or whether there may be a specific uraemic cardiomyopathy, unrelated to the above factors and underlying coronary artery disease or anaemia. Since Bailey et al. first suggested the possibility of a reversible uraemic cardiomyopathy in 1967, there has been a constant trickle of papers supporting this concept. The debate was highlighted by an editorial and two articles in Nephron in 1975 in which Prosser and Parsons were the protagonists and Gueron et al.

the voices of scepticism. Finally all authors of papers on cardiac output in dialysis patients must exclude coincidental pericardial effusion and valvular abnormalities, since they will obviously complicate the haemodynamic findings.

A dominant factor in determining the cardiac output response of regular haemodialysis patients even at rest must be the underlying chronic anaemia. The role of anaemia has usually been acknowledged, but few authors have specifically dwelt on its potential importance and the possible role that differing states of viscosity may play in determining the peripheral resistance and the blood pressure. The Philadelphia group specifically studied this (Kim et al., 1975) by exchange transfusing anaemic dialysis patients. They found that when they increased the haematocrit to 40 per cent, the cardiac output decreased and the diastolic blood pressure and calculated peripheral resistance increased. This cannot simply be an effect of increasing viscosity because Whittaker and Winton (1933) showed that viscosity increases linearly to a haematocrit of about 60 per cent and thereafter rises more steeply. Thus there must be some interaction between viscosity and an abnormal peripheral vasculature, since Kim et al. (1975) found that when the haematocrit was increased from 20 to 40 per cent, the total peripheral resistance doubled, the mean arterial pressure increased from 95 to 110 mm Hg while the cardiac index fell from 5,0 to 3,5 $l/min/m^2$.

Because of the potential importance of the anaemia which is nearly always present in haemodialysis patients, a brief statement of the haemodynamic responses of anaemics without underlying renal disease, both at rest and on exercise, will be given in the next chapter.

CHAPTER 2

HAEMODYNAMIC RESPONSES IN THOSE WITH NON-RENAL ANAEMIA AT REST AND ON EXERCISE

This chapter is intended as an outline of the haemodynamic responses that have been documented in patients with anaemia, unassociated with renal disease, and to provide a background to the type of circulatory responses that may be found in the chronically anaemic haemodialysis population.

2.1 Haemodynamic responses at rest

In their book Guyton et al. (1973) summarize the major circulatory changes that are found in anaemia. There is peripheral vasodilatation due to decreased oxygen transport to the tissues, decreased blood viscosity, decreased resistive load on the heart and, provided that the anaemia is not gross, an increase in myocardial contractility. In their book Wade and Bishop (1962) also review the literature on the haemodynamic findings in chronic anaemia. It seems generally agreed that when the haemoglobin is below 7 gm/100 ml, and provided that the anaemia is not gross (haemoglobin below 3 to 4 gm/100 ml) when myocardial contractility actually decreases, the resting cardiac output is elevated. There is no general agreement on whether the increased cardiac output is due mainly to an increase in heart rate or to an increased stroke volume. Part of the problem lies in the different results obtained when stroke volume is measured recumbent or in the erect position because resting stroke volume is higher when lying than erect. In mild anaemia the cardiac output at rest is within the normal range. The effect of anaemia on the resting blood pressure is variable : in mild anaemia there is usually no change, but when the anaemia

becomes severe there may be a fall in mean arterial pressure (Backman, 1961), because the diastolic pressure drops.

The basic mechanism in chronic anaemia appears to be peripheral vasodilatation due to tissue hypoxia. The arterial oxygen content is lower and it follows from the Fick equation, where oxygen consumption is equal to the product of cardiac output and arteriovenous oxygen difference, that the cardiac output will increase because the venous oxygen content more rapidly becomes zero. There is also a redistribution of the cardiac output at rest with increased blood flow to the cerebral and coronary vessels, and decreased flow to the skin and kidneys. To what extent the increased cardiac output is mediated by increased sympathetic nervous activity or circulating catecholamines is not known. Most of the studies have been done in dogs who have been rendered acutely anaemic (Glick et al., 1964; Escobar et al., 1966). It has been suggested from studies in children (Cropp, 1969) that vasodilatation is accompanied by a transient drop in mean arterial pressure; this results in baroreceptor stimulation and a reflex sympathetic increase mainly in stroke volume and to a lesser degree in heart rate. With the fall in haemoglobin there is a compensatory increase in plasma volume, but most are agreed that the total blood volume remains normal or low, but never high (Jalili and Hindawi, 1962; Backman, 1961). Another compensatory mechanism is a shift to the right of the oxygen dissociation curve facilitating the release of oxygen and hence permitting more efficient tissue oxygen utilization. Many factors are responsible for this shift, but an increase of red cell 2,3, diphosphoglycerate, an increase in carbon dioxide tension and a fall in pH due to the lower buffering capacity and larger proportion of plasma, are probably the most important (Viteri and Torún, 1974).

When the peripheral vasodilatation is reversed by standing or by the

pressor amine, methoxamine, the cardiac output drops to normal (Roy et al., 1963; Duke and Abelmann, 1969). More interesting from the point of view of this Thesis is that the drug induced vasoconstriction is also accompanied by an increase in calculated peripheral resistance and an actual rise in the blood pressure to abnormal levels. In addition after therapeutic correction of anaemia, some patients became hypertensive. It is important to note that these workers were dealing with older patients. This sequence of events is reminiscent of the findings of Kim et al. (1975) in haemodialysis patients where isovolaemic correction of anaemia resulted in a rise in peripheral resistance and diastolic blood pressure. Thus in the older non-renal anaemics and in the dialysis population there may be some structural change in the peripheral vessels resulting in a reduced wall-lumen ratio, which accounts for the unexpected over response of the blood pressure to transfusion, standing and methoxamine.

2.2 Haemodynamic responses to dynamic exercise

Sproule et al. (1960) showed that severely anaemic patients subjected to maximal treadmill exercise could achieve a cardiac output and oxygen consumption that were similar to controls, but that they could sustain these maximal levels of exercise for a much more limited period of time. They had higher lactic acid levels, with severe muscular fatigue and required a longer recovery period to return to baseline levels. When the duration of the exercise period is standardized for both the anaemic patients and the controls (Bishop et al., 1955) there is a higher cardiac output, stroke volume, heart rate and systolic blood pressure at all work-loads studied. Thus severe anaemics on exercise have a lower than normal maximal oxygen consumption, due to a premature achievement of their maximal cardiac output which is also associated with disproportionate tachycardia.

More important for my purpose is the response of patients with moderate anaemia (haemoglobin 8 to 11 gm/100 ml) to dynamic exercise, because this is the haemoglobin range into which most healthy haemodialysis patients fall. With the occasional dissenting report (Beutler et al., 1960) it seems agreed (Viteri and Torún, 1974) that moderate anaemics also have a reduced maximal exercise performance. It is not practical to assess large groups of anaemic patients under maximal conditions nor does it give an accurate indication of their capability to cope with everyday activity. Thus submaximal testing has been introduced (for details see Chapter 4) and it is here that disagreement has arisen. Cotes et al. (1972a) studied iron-deficient anaemics (haemoglobin 8 to 9 gm/100 ml) before and after treatment and found no difference in the heart rate at an oxygen consumption of one litre between the anaemics and matched controls, nor was there an improvement in heart rate in the group treated with iron compared to those on placebo. Davies et al. in a number of publications (1973a, 1973b) studied a group of moderate (mean haemoglobin 9,2 gm/100 ml) iron deficient anaemics at three levels of oxygen consumption, comparing them after iron therapy and to normal controls. Their findings in the moderately anaemic group were of a disproportionate tachycardia which responded to treatment. Viteri and Torún reviewed the results of their group (1974) and they too found reduced submaximal work performance in moderate anaemics. Although the cardiac output is only universally elevated at rest when the haemoglobin is below 7 gm/100 ml, an underlying hyperkinetic circulation will be revealed on exercise with haemoglobin levels between 7 and 11 gm/100 ml (Graettinger et al., 1963). Some of the disagreement may stem from lack of methodological standardization. It is also important to bear in mind that different types of anaemia (iron deficiency versus sickle cell anaemia) and even the same

type of anaemia due to different causes (iron deficiency anaemia due to bilharzia versus that due to menorrhagia) may well have dissimilar responses to standardized exercise even at the same haemoglobin level. The total blood volume at the time of testing is also clearly important. This has been shown in acute blood loss and reinfusions experiments (Murray et al., 1963) in dogs, where cardiac output was inversely related to haematocrit, but directly related to blood volume. Finally, it may be invalid to extrapolate the results of exercise testing to an anaemic individual's daily life, since he may deliberately curtail his activity and hence reduce the circulatory disturbances.

In concluding this chapter on the haemodynamic effects of pure anaemia it must be emphasized that in the moderately anaemic group little systematic work has been done on the blood pressure response to dynamic exercise.

CHAPTER 3

THE PHYSIOLOGY OF EXERCISE TESTING AND THE DOCUMENTED RESPONSES OF HAEMODIALYSIS PATIENTS

3.1 Introduction to the physiology of exercise testing

Obviously formal exercise testing is merely a standardized way of assessing those processes which occur in all of us during everyday activity and which are particularly brought into play when we exert ourselves. These processes are basically a transformation of chemically bound energy into mechanical energy. Biochemically, the main source of this energy is carbohydrate and stored fat. The main carriers of this mechanical energy are adenosine triphosphate and creatine phosphate, and the uptake or release of the phosphate is associated with a gain or loss of energy. Most of this chemical energy is released by aerobic oxidation, but if a certain threshold is exceeded anaerobic processes play an increasingly important role.

This Thesis is concerned mainly with the circulatory response to exercise of haemodialysis patients, but the circulatory responses of normal subjects must first be clarified; these have been well reviewed by Åstrand and Rodahl in their 'Textbook of Work Physiology' (1970), Bevegård and Shepherd (1967) and Rowell (1974). At rest skeletal muscles only receive about 15 per cent of the cardiac output and the peripheral vessels are largely constricted. During exercise vasodilatation occurs and the cardiac output is redistributed, so that the bulk of the increased cardiac output is diverted to the active muscles. In the working muscles

it is largely the accumulation of metabolites such as lactic acid, potassium and phosphate together with changes in tissue pH and carbon dioxide tension (pCO_2) which causes dilatation of arterioles. In addition to the dilatory effect of local metabolites, there is withdrawal of sympathetic constrictor impulses to the vessels in the active areas but enhanced constrictor activity to areas such as the abdominal vessels and the skin, thus allowing redistribution of the blood flow to areas that most need it. In addition to peripheral vasodilatation, there is an increased sympathetic drive to the heart, which together with the withdrawal of parasympathetic activity results in an increased heart rate and, in the erect position, an increase in stroke volume. As a result of the altered autonomic nervous system activity, the increased venous return following on venoconstriction, the pumping action of the muscles and the forced respiratory movements, there is a linear increase in cardiac output with respect to workload up to a maximum level. It appears that in normal subjects the maximal workload that can be achieved is determined more by circulatory than respiratory factors.

During mild to moderate activity, the minute ventilation increases linearly with increasing oxygen consumption, but as workloads approach maximal levels, disproportionate hyperventilation occurs and the slope steepens. What stimulates this increasing ventilation is largely unknown. The comparatively small changes that occur in oxygen tension (pO_2), pCO_2 and the pH of arterial blood are not sufficient to account for the large changes in ventilation. Although the actual mechanisms are not known, it has been suggested that the regulation of respiratory volume takes place by a negative feedback determined primarily by carbon dioxide production in relation to carbon dioxide elimination. In this way the pCO_2 of the arterial blood may via the respiratory centres, determine the magnitude

of ventilation. During anaerobic work the pH of the blood decreases, while during maximal work there is a slight reduction in pO_2, both of which may further increase ventilation. Clearly neuromuscular impulses are important in producing the hyperventilation, but their exact mechanism is unclear. The regulation of breathing during exercise is also reviewed by Åstrand and Rodahl in their book, while a separate chapter in Cotes' book 'Lung Function' (1974) is devoted to this aspect of work physiology. In addition Cotes gives simple guidelines on how to distinguish circulatory and respiratory limitation to effort : basically, those with circulatory disorders will develop a disproportionate tachycardia on exercise with a normal minute ventilation response, while the converse applies to those who have underlying respiratory disorders.

3.2 Exercise testing in regular haemodialysis patients - a review of the literature

There has been a relative dearth of papers on this topic and reviewing the literature from 1960, when regular haemodialysis became a recognized treatment for end-stage renal disease, there have been less than 15 relevant articles. This review has included a MEDLARS search of INDEX MEDICUS covering the past three years. As will be seen later, a number of the papers are in German and French and it is possible that the rather free translations that were available to me may have misinterpreted some of the data; as for the Norwegian paper it was beyond the powers of the average polyglot !

In 1967 Hampers et al., during a haemodynamic evaluation of three dialysis patients before and after nephrectomy, studied the effect of repeatedly raising and lowering a seven pound weight for three to five

minutes from a recumbent position. They demonstrate graphically the effect of this arm exercise both before and after nephrectomy and in relation to dialysis. The original small number of patients was increased to six in a report in 1969 looking specifically at the haemodynamic changes that occurred over a four month period after bilateral nephrectomy. All patients had moderate to severe hypertension with evidence of cardiomegally and all were moderately anaemic. In general, at rest immediately after nephrectomy there was a gradual drop in blood pressure with a decrease in total peripheral resistance but no change in cardiac output. Although plasma renin activity was not measured, it is assumed that the patient's initial hypertension was largely renin dependent. The resting cardiac output levels varied from normal to high and over the four month interval postnephrectomy four of the six patients were progressively able to raise their cardiac output during exercise to about 150 per cent of the resting level. This rise in cardiac output was accompanied in all six patients by a decrease in mean arterial pressure and a minor decrease in calculated peripheral resistance. These exercise results indicate recovery of the patient's hypertensive myocardial damage and an improved ability to cope with physical stress. Although they represent only a minority of dialysis patients, this small series shows the importance of exercise testing and its potential for clarifying haemodynamic problems.

Sill in 1969 studied four patients at rest and on recumbent cycling with increasing workloads until a respiratory quotient of one (RQ 1) had been achieved. No details of the patients are given and there were no controls. The patients showed impaired work capacity (oxygen

consumption of 666 ml/min at RQ1), probable disproportionate tachycardia (120 beats/min at RQ1) and systolic hypertension (SBP 193 mm Hg at RQ1). Although the mean resting blood pressure was 152/103, he makes the point that those who had relatively normal resting pressures had a normal rise on exercise, while those who were hypertensive at rest had an excessive rise. Although his patient numbers are inadequate and the study uncontrolled, his results, as will be seen, are essentially the same as mine. He only gives a resting and exercise stroke volume, but the cardiac output calculated from stroke volume X heart rate would give a resting figure of 13,9 l/min and an exercise level of 21,4 l/min. This seems unlikely. In addition no indication is given of the patients' volume status or whether they were on any drug therapy.

For completeness two papers by McMillan and Evans (1968) and Areskog and Erlanson (1970) should be mentioned. The first article referred to one patient during sitting exercise whose cardiac output was considerably elevated when the arteriovenous fistula was open, but gave no further haemodynamic data. The second is a very brief report in Norwegian.

In one of the best studies to date, Dotremont et al. (1970) while investigating the haemodynamic effect of arteriovenous fistulae, performed supine cycling in five patients under the age of 40 years, with a cardiothoracic ratio of less than 50 per cent, a mean resting blood pressure of 145/90 and a mean haemoglobin of 8,0 gm/100 ml. Hence his patients form a fairly uniform and healthy group. Generally, there was marked tachycardia at the only exercise load studied (35 Watts) and in seven of the nine tests (four patients had repeat tests) it was noted that the diastolic blood pressure and mean arterial pressure

actually decreased on exertion while in only two did it increase. There was a higher than expected cardiac output response and this was attributed to the underlying anaemia, although the resting cardiac output was normal. Together with the fall in mean arterial pressure on exercise there was a fall in calculated peripheral resistance. Again no body volumes were mentioned.

Payne et al.(1972) studied the exercise-induced haemodynamic effects of arteriovenous fistulae in eight patients with a mean age of 33 years and haemoglobin of 7,0 gm/100 ml. They observed the effect of fistula compression on cardiac output, heart rate, central venous pressure and arterial pressure during submaximal supine graded cycling at two or three levels of increasing workload of five minutes duration. They concluded that the arteriovenous fistula produces little haemodynamic disturbance, but of greatest interest are the results obtained on graded exercise with the fistula open. They showed a decreased work capacity with markedly lowered estimated maximal oxygen consumption, disproportionate tachycardia, and a cardiac output that rose from a resting level of 8 l/min to 16 to 18 l/min at an approximate (because not measured) oxygen consumption of 1,5 l/min which is characteristic of a markedly hyperkinetic circulation. The mean aortic pressure rose tremendously from 110 mm Hg at rest to 150 mm Hg at an oxygen consumption of 1,5 l/min. These authors state that the increase in arterial pressure is similar to that expected in normal individuals and quote Åstrand's Textbook as reference. This is clearly incorrect, both as an interpretation of Åstrand's work and also of the normal response as will be seen from my own control data. They show the heart rate systolic blood pressure product of their patients at rest and on exercise. Extrapolating from these figures and the heart rates, the mean systolic

pressure at rest was 155 and on exercise 223 mm Hg, confirming the accelerated rise of pressure on exercise. However, half the patients had a resting systolic pressure of 160 or more. The heart rate systolic blood pressure product is a good index of myocardial oxygen consumption and hence indirectly the work of the heart. Although the product is grossly elevated on exercise in their patients, they do not comment on the potential adverse significance of this finding in terms of cardiovascular mortality.

In an article in French in 1972, Mallion et al. studied the maximal work capacity of nine male and five female dialysis patients. The mean maximal workload achieved by the two sexes was approximately 80 and 70 Watts respectively which is very poor. The main point of the paper was that at least two patients developed ischaemic ECG changes at these levels with heart rates of 150 and 180 beats/min. and pressures of 210/120 and 195/95 respectively.

One of the possible reasons that exercise testing in dialysis patients is so little performed in the English-speaking world is that most of the available literature comes from Europe and is in German or French. The next three papers in chronological order are in German. Hensel et al. in 1973(a) studied 10 patients with recumbent cycling and compared them both to a group of physically fit and a group of sedentary subjects. The mean age of the dialysis group was 25 years with a mean haematocrit of 27 per cent, and five of the 10 patients were on antihypertensive therapy. The 10 patients were split into two groups : those who could manage a workload of 100 Watts for five minutes and those who could not achieve this level. The blood pressure responses were varied; some rose alarmingly while some actually fell on exercise and there was no clear

relationship between the resting pressure and the response to exercise. There was generally a hyperkinetic cardiac output response to exercise, and an abnormally low response was only seen in two patients who had latent cardiac failure. However, the increase in heart rate for the 10 patients (+ 68 per cent) was approximately the same as sedentary controls (+ 69 per cent) and athletes (+ 60 per cent).

Sill, who published one of the earliest papers, combined with colleagues in 1973 to study the work capacity of dialysis patients before and after transfusion. He used the same method of recumbent cycling, standardizing the exercise load to produce a respiratory quotient of one. They transfused 10 patients more or less isovolaemically from an initial mean haematocrit of 21 per cent to 38 per cent and restudied their exercise responses. Following transfusion six patients showed improved performance, while four remained the same. It is noteworthy that those who did improve, did not reach normal expected levels of work performance. Of interest, the tachycardia decreased in all and in the group that improved there was a fall in pulmonary artery pressure on exercise, but an actual rise in diastolic blood pressure. This is reminiscent of the transfusion experiments reviewed by Kim et al. (1975).

Lange et al. published in German in 1973 and then as an abstract in English in 1974 a study on anaerobic metabolism during exercise in dialysis patients with differing degrees of anaemia. Nine patients (no patient data given) had blood lactate, pyruvate, acetoacetate and β-hydroxybutyrate levels measured at rest, after bicycle exercise and during the recovery period. The group was first tested when their mean haemoglobin was 7,6 gm/100 ml and again after transfusion to a haemoglobin of 10,2; the blood levels were compared to those in healthy

volunteers. After exercise while severely anaemic excess lactate was greater than when moderately anaemic. No further changes occurred after increasing the haemoglobin from 10,2 to 12,4 gm/100 ml. They concluded that anaemia was an important limiting factor of work performance and was accompanied by increased blood levels of anaerobically produced metabolites.

Very few observations on the respiratory response to exercise in dialysis patients have been made apart from the mention of minute ventilation in the German papers by Sill (1969) and Hensel et al. (1973). Crosbie and Parsons in 1974 investigated the cardiopulmonary function of six dialysis patients at rest and during a single workload sitting on a bicycle after they had gained more than five kg excess weight over a period of less than four days. They showed that the patients' lungs continued to transfer gas to the arterial blood normally even when they contained a fourfold increase in their water content. The gas exchange only deteriorated when heart failure and hypoxaemia supervened and this was most clearly shown by the exercise response. The average age of his patients was 46 years and the mean haemoglobin 8 gm/100 ml . Cardiac output was measured by indicator-dilution techniques using isotopes and not dye. The resting values were generally high and, with the exception of the two cases who were in heart failure, became even more hyperkinetic on the mild exercise to which they were subjected. No further circulatory data was given.

Mallie et al. in 1974 made the interesting observation that maximal oxygen consumption levels were attained in 15 male patients aged 23 to 40 years, at submaximal heart rates. However, no mention is made of the blood pressure response during exercise, because, as will be seen, hypertension may through the baroreceptor reflex suppress the anticipated

tachycardia. They also showed a reasonable correlation ($r = 0,51$, $p = 0,01$) between maximal oxygen consumption and haematocrit level.

Dutz presented a paper at the World Nephrology Congress in Florence in 1975 in which he compared the work capacity of a large number of dialysis and transplant patients. No real patient details were given, but he found that the dialysis patients only had 43 per cent of normal work performance and in addition made the surprising observation that females performed better than males.

A fitting conclusion to this chronological survey was a paper written by Merrill in 1975 (his group produced the initial papers on arm exercise in 1967 and 1969) on 'recommendations for evaluation of the cardiovascular response of dialysis patients' in which he states, without giving any details, his prejudice for performing routine exercise testing since this measures 'the capacity of the whole organism, not just the heart'.

3.3 Unresolved problems arising from this review

Apart from the paucity of literature on exercise in dialysis patients the subject is bedevilled by the lack of standardization of methodology and the type of patients tested. Most of the exercise has been done recumbent and only two papers discuss sitting exercise. With one exception (Payne et al., 1972) only a single workload has been used and the duration of exercise at this one load varies from five to 12 minutes. Oxygen consumption at a particular workload is rarely measured and this is important as the mechanical efficiency of chronically ill patients may vary. Controls are not always used and results have to be compared with others' normal data. In regard to the type of patient tested there is

clearly a wide spectrum of the degree of rehabilitation and basic healthiness of the patients. Age, sex, body size, the patient's circulating blood volume and antihypertensive drugs are all important in determining the exercise response and these facts are seldom specifically mentioned. In those studies where cardiac output and blood pressure measurements are performed, body volumes and plasma renin activity are not included, nor has the integrity of the cardiac reflexes been assessed.

In spite of these criticisms certain trends emerge. There is clearly decreased work capacity; most but not all (Hensel et al., 1973) find a disproportionate tachycardia and the circulation is hyperkinetic, sometimes at rest but usually on exercise. Much confusion arises in regard to the blood pressure response to exercise. Not only are controls seldom performed, but the patients' resting values vary considerably and no attempt is made to look separately at normotensive and hypertensive individuals. Although most develop a hypertensive response, Dotremont et al. (1970) found a hypotensive response in seven of the nine exercise tests performed. Some found a correlation (Sill, 1969) between the resting level and the exercise response, whereas others (Hensel et al., 1973) found no correlation. The relationship between a hypertensive response and the heart rate response has not been explored, but the possibility of reflex slowing is suggested by Mallie et al. (1974) whose patients achieved maximal oxygen consumption levels at submaximal heart rates.

Apart from the study of Crosbie and Parsons (1974), information on the ventilatory response of these patients is very scanty. Even some of Crosbie's data must be viewed with reserve, since his patients were performing at a very low workload (mean of 34 Watts and assumed oxygen

consumption of about 650 ml/min) and the alveolar-arterial oxygen gradient requires an oxygen consumption in excess of 1,5 l/min for accurate interpretation (Jones et al., 1966). Again all the circulatory studies and the few respiratory ones are done on very small numbers of patients, with the exception of Dutz (1975) where the full data is not yet available.

Finally, the role of anaemia in the overall exercise response is not clearly understood. It is generally agreed to contribute to the decreased work capacity, the hyperkinetic circulation and anaerobic metabolism, but to what extent is uncertain. In their study Sill et al. (1973) could only show improved work capacity in 60 per cent of the patients after transfusion. Thus anaemia remains the 'eminence grise' behind these haemodynamic studies, but its exact relationship to the prime movers of circulating volume, cardiac output and peripheral resistance is not clear.

CHAPTER 4

PRACTICAL ASPECTS OF EXERCISE TESTING

4.1 Introduction

There are various types of exercise test, differing both in how they are performed and in what parameters are measured. These differences make comparative studies difficult and there is great need for work physiologists to standardize not only the test used, but also the measurement and presentation of data.

The maximal oxygen consumption ($\dot{V}_{O_2}$ Max.) when actually measured is one of the few generally accepted criteria of physical performance. However, maximal testing is not easily applicable to clinical medicine, since there is the discomfort to the patient of being driven to exhaustion as well as a potential hazard in the chronically ill. Thus there is a recent tendency to use various submaximal tests and either to extrapolate from heart rate to $\dot{V}_{O_2}$ Max. or to specify the heart rate and/or minute ventilation achieved at a fixed level of oxygen consumption. If the latter method is used, specifications should be made at two or more oxygen consumption levels in order to assess accurately the rate of rise of the heart rate or minute ventilation as exercise progresses.

The different ways of performing exercise tests have included the treadmill, lying and sitting cycling, the step test and skiing. Shephard et al.(1968) in the Bulletin of the World Health Organisation analysed the pros and cons of the treadmill, the bicycle and step tests . They felt that there was little to commend submaximal exercise on the treadmill

and recommended sitting cycling for laboratory tests where arm immobilization was required for haemodynamic measurements, and the step test for field surveys of work performance. Anxiety and learning were least on the bicycle ergometer, but significant anaerobic metabolism developed at loads of more than 55 per cent of aerobic power. Apart from the apparatus used, there has been no agreement on how the workloads should be increased. There are two basic methods : firstly, to exercise at a single fixed workload until a steady-state is achieved, allow the patient to recover and then to repeat the test at another workload. The other method is to increase the workload every minute until maximum effort is reached and then make recordings. Recently certain authors (Shepherd et al., 1968; Cotes, 1972 b) have recommended progressive work tests, whereby the workload is increased every two to four minutes, until three or four workloads of increasing severity have been performed; recordings are made in the last minute of each workload. This raises the problem of the steady-state condition, i.e. a work condition where oxygen uptake equals the oxygen requirement of the tissues, and the heart rate, cardiac output and pulmonary ventilation have reached fairly constant levels. Most of the circulatory changes reach a steady-state in the first two minutes, but such ventilatory parameters as the respiratory quotient may take three to five minutes to become stable. Ten minutes is too long and one to two minutes too short, so that some compromise between four and six minutes of exercise per workload produces a true steady-state without unnecessarily prolonging the duration of the test.

Under laboratory conditions measurements can be made of the minute ventilation, respiratory rate, heart rate, electrocardiograph, blood

pressure and the percentage expired CO_2 and O_2 without taking any blood, i.e. a bloodless test. If invasive methods are used these measurements can be extended to cardiac output, blood gas analysis and direct pressure measurement. Bruce et al. (1972; 1974) have done much work in the field of hypertension and ischaemic heart disease and have advocated routine sphygmomanometer readings during exercise. Previously blood pressure was seldom recorded unless an arterial line was in situ.

4.2 External conditions influencing exercise tests

These are numerous, and what follows is merely a summary of the recommendations of Åstrand and Rodahl (1970). It is difficult to standardize all of them, but particularly where different groups are being compared, attention should be paid to :

(i) Age of the subjects.

(ii) Their sex.

(iii) The body dimensions. Some feel that simple height and weight measurements are not sufficient and that an estimation of the dominant muscle group, e.g. thigh and calf in cycling, should be added (Spiro et al., 1974).

(iv) The degree of regular physical activity and training.

(v) Other external conditions such as the ambient temperature and relative humidity, the clothing worn and the timing of the test in relation to meals should also be standardized as far as possible.

(vi) Although there is no circadian rhythm with exercise testing, it is desirable that all subjects should be tested at the same time of day.

(vii) The exercise posture, whether recumbent, sitting or standing, is of particular importance in haemodynamic measurements and striking differences are noted between the erect and the supine position.

Before any exercise test is performed, certain commonsense precautions should be observed, since fatalities during the test have been recorded. These deaths have occurred mainly during exercise for the investigation of chest pain. Thus all subjects, unless they be healthy young volunteer controls, should be examined clinically and a resting electrocardiograph taken before the test. The ECG should be continuously recorded and the test stopped if abnormalities occur.

4.3 Exercise testing at Charing Cross Hospital

4.3.1 Technique

Our system has been largely adapted from that of Cotes (1972b), Wasserman et al. (1973) and Spiro et al. (1974). In general, submaximal recordings are made, but maximal effort tolerance can readily be measured if required. The exercise is done in the sitting position on a bicycle ergometer and three or four increasing workloads are performed, each workload lasting four minutes. Recordings are made during the fourth minute of each load. Steady-state experiments have shown that the circulatory and ventilatory parameters measured, with the possible exception of the calculated respiratory quotient, remain stable during this time.

The subjects are clinically examined and an ECG performed prior to

the test. Height, weight, age and sex are recorded, and the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are measured on a VERTEK VR 5000 Lung Function Computer. The maximum predicted heart rate is calculated by Åstrand's formula [Predicted maximum heart rate = 210 - (age x 0,65)], and care is taken during the test not to approach this figure, especially in patients. In addition the ambient temperature, pressure and relative humidity are recorded. This information is entered on a datum sheet which is later submitted for computer analysis. The regular dialysis patients were submitted to a far more rigorous work-up and the details of this will be presented in the next chapter.

The subject is then seated on the bicycle ergometer (Lanooy, Lode Instrumenten, Gonigen) and care is taken to ensure that the saddle height is adjusted to allow almost complete extension of the legs to the pedals. In a non-invasive test the subject simply grips the handlebars, but during invasive tests one arm rests on a supporting board. The procedure is fully explained to the patient and he is advised about chest pain, palpitations and muscle fatigue. Blood pressure is recorded with a sphygmomanometer that is adjustable, so that the base of the mercury column is approximately at the level of the right atrium. Electrodes for respiratory rate, heart rate and ECG are placed, and the subject allowed to become accustomed to the mouthpiece and noseclip before exercise commences. At eye level is a revolution counter and the patient is requested to maintain his pedalling speed throughout the test between 50 and 70 revs/min. Minute ventilation is measured by a Dry Gas Meter (Parkinson Cowan Measurement) through which the inspired air is drawn while the expired gas is drawn through a mixing chamber and drying tube to a Uras 2 Infra-red Gas Analyser for carbon dioxide

(Hartmann and Braun) and to a Portable Oxygen Analyser (Taylor, Servomex). Both these gas analysers are calibrated before each test and the readings of expired percentage of CO_2 and O_2 as well as minute ventilation are displayed on separate digital voltmeters. The heart rate, respiratory rate and ECG is recorded by a Hewlett-Packard Monitor, which is connected to an Elcomatic EM 70 ECG recorder.

The test is started with a preliminary period where the subject is cycling to overcome the inertia of the machine, but not actually working. This period is called rolling basal or 0 Watts. Thereafter at least three progressive workloads are imposed. Heart rate, respiratory rate, an ECG strip, expired percentage O_2 and CO_2 and minute ventilation are recorded during the fourth minute of exercise, while blood pressure readings are taken between two or four minutes. The test is terminated if the patient develops chest pain, ECG changes of ischaemia (Minnesota Code), a heart rate rapidly approaching the maximum predicted level or severe hypertension. After the test a brief recovery period ensues during which heart rate, ECG and blood pressure are observed and all symptoms that occurred during exercise are noted.

4.3.2 Recording, calculation and presentation of the data

A separate datum sheet is used for each subject which incorporates not only the baseline information previously mentioned, but is so devised that at each work level the following measurements are made during the final steady-state minute : heart rate, respiratory rate, and the expired percentage O_2 and CO_2 are separately recorded on three occasions in addition to an ECG and respiratory rate strip. Minute ventilation is noted at the beginning and the end of the minute. The information

from each datum sheet is fed into a CDC 6600 Computer (University College of London Computer Centre) which then averages the heart rate, respiratory rate, minute ventilation and expired percentage O_2 and CO_2 for each workload. The computer printout includes calculated tidal volume, oxygen consumption, carbon dioxide production and respiratory quotient. In addition it presents graphically the relationship of oxygen consumption to heart rate, minute ventilation and workload, and provided there are at least three workloads, excluding the rolling basal, it calculates the line of closest fit for heart rate, minute ventilation and workload against oxygen consumption and gives the regression equation. If invasive methods are added to this basic bloodless test, more sophisticated calculations can be performed, but these will be detailed later.

In terms of presenting results many authors merely give one figure for heart rate and minute ventilation at a fixed oxygen consumption, e.g. 1,0 or 1,5 l/min. However, this does not give an indication of the rate of change of these parameters during exercise, and particularly for studies where various groups of subjects are being compared, heart rate and minute ventilation should be presented at two or three levels of oxygen consumption. This is easily performed by substituting differing levels of oxygen consumption e.g. 0,75, 1,0 and 1,5 l/min into the calculated regression equations. This allows standardization of results without having each subject perform identical workloads.

Finally, the terms 'respiratory quotient of more than one' (RQ > 1) and 'mechanical efficiency' which will appear frequently in subsequent chapters, must be clarified. In bicycle exercise anaerobic metabolism occurs earlier than in the other forms of exercise testing and this is

seen when the RQ exceeds one. Anaerobic metabolism (RQ > 1) is due to a fixed acid, such as lactic acid, accumulating in the circulation and acting on the plasma bicarbonate with a drop in the blood pH and disproportionate hyperventilation. Thus many investigators have used RQ 1 as a reference point for comparing subjects' responses to exercise. In order to compare the mechanical efficiency of work, some point on the oxygen consumption workload regression equation is chosen and in this instance since all the patients managed at least 50 Watts efficiency has been expressed as the $\dot{V}_{O_2}$ in ml/min at 50 Watts.

CHAPTER 5

BACKGROUND TO DIALYSIS TECHNIQUES AND THE CHOICE AND INVESTIGATION OF PATIENTS

The first end-stage renal failure patients at Charing Cross Hospital were accepted for hospital-based dialysis in 1964 and the longest surviving patient has now been on dialysis for 12 years. Regular haemodialysis is combined with transplantation for the treatment of end-stage renal failure, but, because of problems with cadaver transplantation in the United Kingdom, the emphasis is on long-term dialysis. Home dialysis was introduced in 1967 and current policy is to train all newcomers in the hospital for three or four months before they are installed at home. The hospital centre is thus primarily for home training but it also provides a back-up for patients with problems. This policy is illustrated by current (August, 1975) figures showing that 90 patients are dialysed at home and only 20 to 25 in the hospital. The patients are seen at regular intervals at a home dialysis clinic. The bulk of the patients are fully rehabilitated and working. So much emphasis is placed on full employment, that it was at times difficult to induce some patients to take a morning or a day off work to perform the exercise test.

The patients dialyse twice weekly for a total of 20 hours a week on Meltec Multipoint 1 m^2 Kiil dialysers. The water is softened and proportioned by Dyalade Single Patient machines to a final dialysate concentration containing 140 m Eq/l sodium, 2,0 m Eq/l potassium, 106,5 m Eq/l chloride, 0,5 m Eq/l magnesium, 3,5 m Eq/l calcium, 40 m Eq/l acetate and 200 mg/100 ml glucose. The majority of patients have arteriovenous

fistulae which they cannulate themselves but shunts are also used when there is difficulty with vascular access. Most are on a mildly protein (1 gm/kg/day) and salt restricted diet, but fluid intake is determined by their blood pressure and residual renal function. The only routine therapy is multivitamin and folic acid tablets, supplemented by iron infusions every six to 12 months.

Initially, I did not know personally any of the patients and they were chosen for me by the sister-in-charge and the renal social worker. I only specified that the patients should be fully rehabilitated, below the age of 45 and on no cardiovascular drugs. In addition some should have been on dialysis for less than a year and some on for many years. The protocol for the investigation of the patients was approved by the Charing Cross Hospital Medical School Ethics Committee and since the initial negotiations were done through the renal social worker, any patients who were not willing to undergo the test, were able to drop out without embarrassment.

Each patient was assessed according to a standard investigation sheet. Particular emphasis was paid to the blood pressure, heart rate, the degree of anaemia and circulatory volume. In each case routine blood tests, a resting ECG and a single inspiratory chest X-ray was done. Drug therapy, urinary output and the time relationship of the patient to dialysis was noted. Evidence of abnormal cardiovascular reflexes or the presence of a haemodynamically important arteriovenous fistula was documented in all cases.

A total of 40 haemodialysis patients were tested, some of them on two or more occasions. Certain clear patterns of response to exercise emerged from this group, but it should be stressed that these 40 patients are probably healthier and better rehabilitated than many dialysis patients and that I do not have information on those who are chronically ill.

CHAPTER 6

THE SENSITIVITY AND REPRODUCIBILITY OF EXERCISE TESTING AND SPHYGMOMANOMETER BLOOD PRESSURE

In order to be able to use exercise testing either as a tool for physiological investigation or as a method of patient assessment and follow-up, it must be both sensitive and reproducible. All blood pressure measurements were made by myself using a standard sphygmomanometer, and since a large part of this Thesis is based on blood pressure results, this technique also needs validation. Because the study is largely a comparative one, this validation must apply both to the controls as well as to the patients. There are no 'normal' values for the circulatory and ventilatory responses to exercise, because, as mentioned, these vary with age, sex, body dimensions and physical training. Thus I have chosen my control group from hospital personnel leading a largely sedentary life and have tried to match them as closely as possible with the patient groups.

6.1 Exercise testing

All the tests, both for the controls and the patients, were performed in a standard fashion, but clearly some subjects were able to do better than others. However, the results have been expressed in such a way that allows direct comparison, viz. heart rate at various levels of oxygen consumption, H.R./$\dot{V}_{O_2}$ 0,75, 1,0, 1,5. No statistics are given, because the numbers tested to validate the methods are too small for paired 't' test analysis, and a coefficient of variation is irrelevant, as the technical details of exercise tests vary from laboratory to laboratory.

6.2 Reproducibility in the controls

Since all the patients were studied over a six month period, some of the controls had repeat tests performed to demonstrate what variability might occur during this time. Table I shows the data on four males and one female (N_{17} and $N_{17}R$) whose ages ranged between 24 and 34 years, and who had been tested over intervals varying from one to four months. The heart rate (H.R.) and minute ventilation ($\dot{V}_E$) are shown at two levels of oxygen consumption ($\dot{V}_{O_2}$ 1,0 and 1,5 l/min), and mechanical efficiency is calculated from the oxygen consumption/workload regression equation by deriving the oxygen consumption in ml/min at a workload of 50 Watts. The actual values are given as well as the maximum change (Δ) between the tests. It must be borne in mind in assessing reproducibility that the subject may have changed between the tests and one cannot assume that they are necessarily in the same state on each occasion. The first control N_{23} shows disproportionate tachycardia on both occasions. He is a healthy young doctor and presumably has the hyperkinetic circulation syndrome initially described by Holmgren et al.(1957). Although he has been excluded from future control studies, he illustrates that the exercise test is equally reproducible at rapid heart rates.

6.3 Reproducibility and sensitivity in patients

The situation with the patients is more complex, because the variablity of the exercise test will depend on how stable their health is and particularly on how long they have been on dialysis. Thus they are arbitrarily divided into two groups, those who had been on dialysis for less than a year and were expected to show a steady improvement, and those who had been on for more than a year and should be more stable. In addition one stable patient is shown over a six month period of repeated

Table I - Reproducibility in Five Controls

Subject	Intervals (months)	$H.R._{1,0}$	$H.R._{1,5}$	$\dot{V}_{E_{1,0}}$	$\dot{V}_{E_{1,5}}$	$\dot{V}_{O_2}$ at 50W (ml/min)
N_{23}	1	141	159	20	31	1182
$N_{23}R$		143	164	24	34	1112
N_{15}	2	97	119	30	45	1016
$N_{15}R$		95	118	29	43	986
N_5	4	104	129	27	41	1180
N_5R		98	127	24	37	1122
N_{16}	4	115	146	33	53	1010
$N_{16}R$		108	145	31	47	1011
N_{17}	4	130	160	28	40	948
$N_{17}R$		130	164	28	43	981

MaxΔ $HR_{1,0}$	7	Max Δ $HR_{1,5}$	5
MaxΔ $\dot{V}_{E_{1,0}}$	4	Max Δ $\dot{V}_{E_{1,5}}$	6
Max Δ $\dot{V}_{O_2}$ at 50W	70		

testing. In the patient groups then we are assessing both reproducibility and sensitivity. 'Sensitivity' here means the ability of the test to record slight changes in the condition of the subject.

6.3.1 Patients on dialysis for less than a year

Five male patients, age range 19 to 35 years, were tested twice, on each occasion either before or between dialysis, so that the effect of dialysis itself is eliminated. Table II shows the heart rate, minute ventilation and efficiency, as well as the interval between testing and their duration on dialysis at that time. Note that heart rate and minute ventilation is assessed at $\dot{V}_{O_2}$ 0,75 and 1,0 l/min , because the patients were not able to attain a comparable exercise load to the controls. The maximum change of $H.R._{1,0}$ of the controls (Table I) is seven beats/min and thus patients G.D. and A.S. show distinct improvement, whereas probably only G.D. improves at a $\dot{V}_{E_{1,0}}$. In terms of mechanical efficiency compared to controls, G.D. and D.C. both have a change greater than 70 ml/min , but are moving in opposite directions. D.C. shows borderline improvement both in heart rate and minute ventilation and probably overall has improved on the second occasion. The two patients who showed no change, B.B. and G.F., again illustrate the remarkable reproducibility of exercise testing.

6.3.2 Patients on dialysis for more than a year

Shown in Table III are four male patients, age range 25 to 36 years, who had been on dialysis from four to nine years and were expected to be stable and had developed no intercurrent illness between testing. In fact their heart rates and minute ventilation are even more reproducible than the controls. However, inexplicable in both P.R. and K.E. is the striking change in efficiency above the control maximum Δ. The only

Table II - Reproducibility and Sensitivity in Five Patients on Dialysis for Less than a Year

Subject	Interval (months)	Duration dialysis (months)	$H.R._{0,75}$	$H.R._{1,0}$	$\dot{V}_{E_{0,75}}$	$\dot{V}_{E_{1,0}}$	$\dot{V}_{O_2}$ at 50W (ml/min)
B.B.	0,1	2,0	138	157	23	32	864
		2,0	135	152	26	37	878
G.D.	1,0	5,0	126	142	29	38	901
		6,0	108	123	22	30	1084
D.C.	3,0	2,5	124	136	23	30	1206
		5,5	117	130	19	25	1113
G.F.	4,5	4,0	126	146	26	35	930
		8,5	124	148	23	32	940
A.S.	5,5	1,0	162	187	30	44	853
		6,5	143	169	28	40	909

Table III - Reproducibility in Five Patients on Dialysis for More than a Year

Subject	Interval (months)	Duration dialysis (months)	$H.R._{0,75}$	$H.R._{1,0}$	$\dot{V}_{E_{0,75}}$	$\dot{V}_{E_{1,0}}$	$\dot{V}_{O_2}$ at 50W (ml/min)
L.S.	2,0	99	118	139	19	27	950
		101	116	135	20	28	955
P.R.	3,5	108	107	117	21	29	1205
		111,5	102	115	22	30	1119
K.E.	4,5	48	114	132	23	33	927
		52,5	113	130	26	36	1060
D.P.	5	58	111	130	19	26	979
		63	112	128	19	26	1022

reasonable explanation is that efficiency is calculated at one point only of the regression line and that this one point does not represent the overall slope and intercept of the line.

6.3.3 Change in a stable patient over six months

Table IV illustrates a single male patient, R.B., aged 20 years, who had been on dialysis 11 months when first tested and was subsequently retested on three other occasions. On each occasion he was tested on the same day between dialysis. His haemoglobin (Hb), serum creatinine (Cr.) and measured cardiothoracic ratio (C.T.R.) is given, as well as the oxygen consumption achieved at a 75 Watt workload. His heart rate and minute ventilation response is also shown. On the first occasion tested his Hb was 6,0 gm/100 ml and his C.T.R. 41 per cent and this may account for the differences in oxygen consumption, efficiency and heart rate when compared to the three subsequent occasions. However, in the latter when Hb and C.T.R. are much the same, the oxygen consumption, efficiency, heart rate and minute ventilation are remarkably constant.

6.4 Conclusions

These results on the control and patient groups show little variability between testing, at least over a six month period, provided the subjects' physical condition remains stable. The test is also sensitive enough to indicate real change and to indicate whether this change is mainly circulatory or respiratory. Thus it would be eminently suitable for long-term follow-up and assessment of physical rehabilitation.

6.5 Reproducibility of blood pressure measurements

As will be seen later one of the cornerstones of this Thesis

Table IV - Reproducibility in a Stable Patient over Six Months

Interval (Months)	Hb (gm/100ml)	Cr. (mg/100 ml)	C.T.R. (%)	$\dot{V}_{O_2}$ (ml/min) at 75 Watts	H.R. 0,75	H.R. 1,0	$\dot{V}_E$ 0,75	$\dot{V}_E$ 1,0
0	6,0	11,6	41	1132	129	152	20	31
1,0	5,7	12,7	47	1304	122	145	20	27
2,5	5,7	16,0	48	1297	117	142	22	31
6,0	5,7	11,7	45	1292	124	145	18	26

rests on the different blood pressure responses obtained during exercise. Most patients had arteriovenous fistulae and it was considered unjustifiable to perform separate arterial puncture for direct blood pressure readings. A recent publication (Evans and Kerr, 1975) showed that of 155 consecutive patients who had radial artery cannulations during anaesthesia, 33 had signs of arterial occlusion immediately postoperatively, but by the end of the follow-up period blood flow had returned in 19 of the 22 occluded arteries. Dialysis patients may in time need all their peripheral arteries if problems with vascular access arise; thus even a small risk of permanent occlusion is unacceptable. For these reasons unless an arteriovenous shunt was present, all blood pressure measurements were made by myself using a sphygmamanometer adjusted to right atrial level and using the same cuff of standard adult size.

In order to validate my measurements, the first step was to compare the indirect readings with intra-arterial pressure taken simultaneously and over as wide a range as possible. Only three patients with arteriovenous shunts were obtained in whom simultaneous direct and indirect measurements could be made. The indirect measurements were taken in the opposite arm. The technique of direct measurement was by connection of the arterial end of the shunt to an SE pressure transducer and recording a slow, fast and electrical mean. The venous side of the shunt was clamped during this procedure.

Figure 1 shows on an interrupted, but otherwise identical scale, the results in these three patients of indirect systolic blood pressure plotted against direct. There is obviously an excellent correlation ($r = 0,97$, $p < 0,00$ but it must be noted that the indirect method progressively underestimates

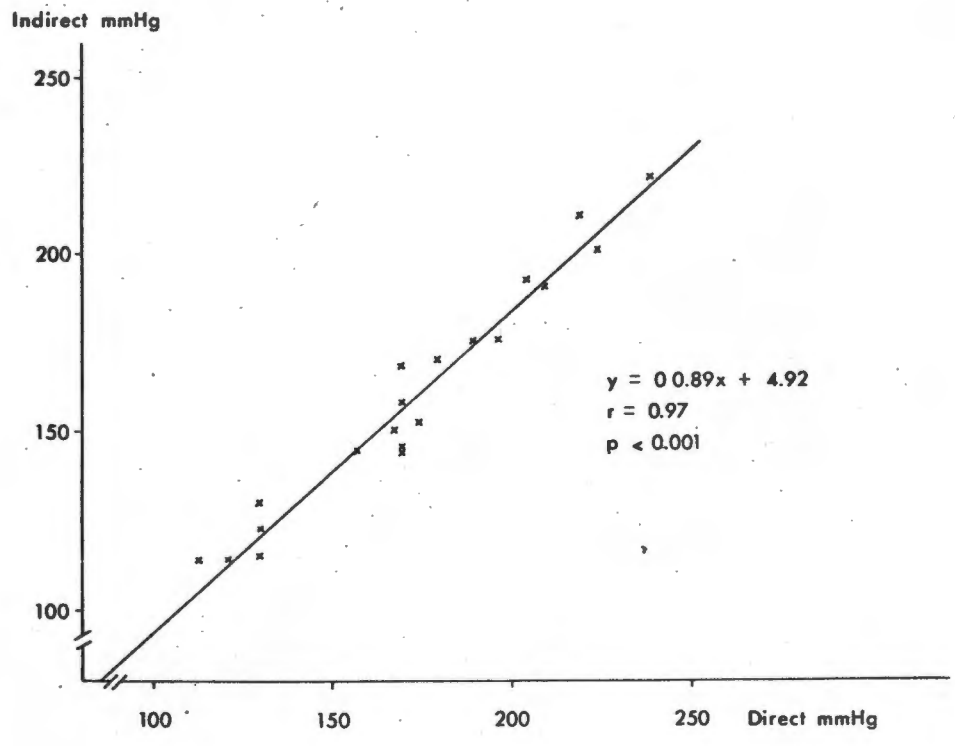

Figure 1 - Indirect vs Direct Systolic Blood Pressure

the true pressure and, as will be seen later, this occurs as the exercise load increases. Nonetheless, cuff systolic blood pressure at least accurately reflects changes in true systolic pressure.

Figure 2 shows the results of indirect diastolic blood pressure plotted against direct. Here the results are much less satisfactory and it was a definite impression that on exercise it became increasingly difficult to distinguish between muffling (Phase 4) and disappearance (Phase 5), the latter being the more accurate. Although the correlation is reasonable ($r = 0{,}58$, $p < 0{,}01$), at lower pressures the indirect method tends to underestimate the direct, while the converse happens at higher levels. However, if one accepts the obvious errors, the indirect

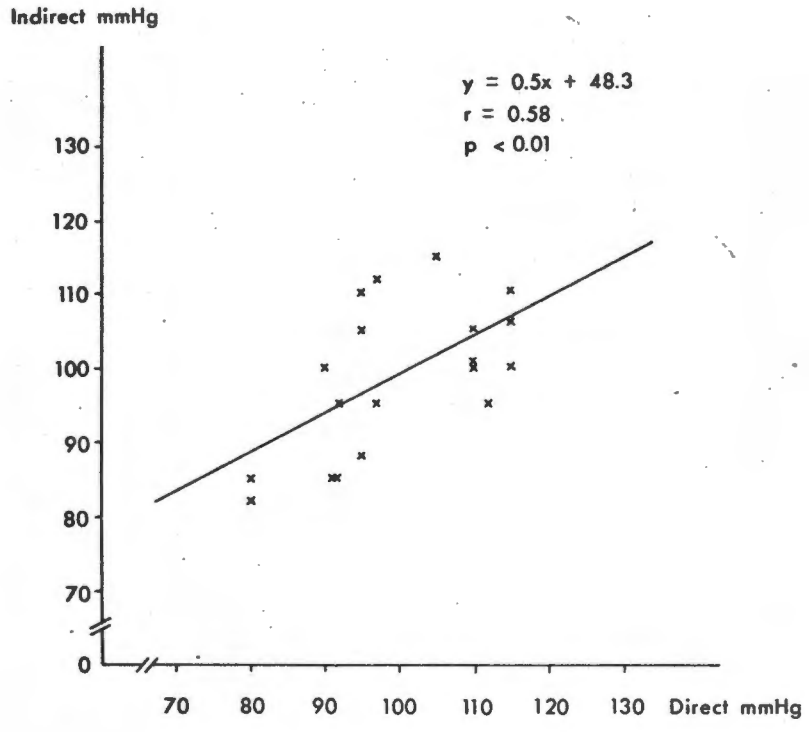

Figure 2 - Indirect vs Direct Diastolic Blood Pressure

diastolic readings are useful in detecting major changes as exercise progresses.

In order further to evaluate the reproducibility of the indirect blood pressure measurements, Table V shows the pressure of four out of the five controls who had repeat exercise tests (see Table I). As mentioned earlier in this chapter, the control subjects should have remained relatively stable over a four month period and the readings are comparable because they were retested at the same workloads. It can be seen that the agreement in the systolic blood pressure readings is very good (Maximum difference (Δ) = 13 mm Hg) and that there is no gross discrepancy in the diastolic (Maximum difference = 20 mm Hg).

Table V - Reproducibility of Sphygmomanometer Blood Pressure in Four Controls

Patient	Interval (months)	Workload (Watts)	SBP		DBP	
			(i)	(ii)	(i)	(ii)
N_{23}	1,0	0	133	120	71	80
		35	145	135	70	66
		70	160	165	72	75
		105	173	174	60	60
N_5	4,0	0	110	105	60	74
		35	125	115	70	72
		70	140	140	60	72
		105	155	158	60	70
N_{16}	4,0	0	100	108	60	70
		35	130	122	60	65
		70	150	155	70	70
		105	160	165	60	70
N_{17}	4,0	0	110	-	-	-
		75	130	135	70	75
		105	150	145	50	70

MaxΔ SBP = 13 mm Hg

MaxΔ DBP = 20 mm Hg

A number of patients had repeat exercise tests performed (Tables II and III) and one patient was retested four times. The reproducibility of the blood pressure readings was usually very good, both for the systolic and the diastolic. However, there were minor differences in body weight suggesting differences in body volume composition which may have been responsible for a greater variation than was seen in the controls. Some of the blood pressure variations will be shown in more detail in later chapters when the importance of the body volumes is discussed.

6.6 Conclusions

The good correlation between the indirect and direct measurement of blood pressure and its reproducibility on repeat testing, establish the reliability of the sphygmomanometer method, at least for systolic pressure, but it is important to remember that the cuff reading progressively underestimates the true reading. Although less emphasis will be placed on the diastolic readings because of the difficulty, especially on exercise, of determining exactly when Phase 4 and Phase 5 occur, the measurements are probably a reasonable indication of major response differences.

CHAPTER 7

THE EFFECT OF DIALYSIS, THE ARTERIOVENOUS FISTULA AND THE AUTONOMIC NERVOUS SYSTEM ON THE RESPONSE TO EXERCISE

In all haemodynamic studies of dialysis patients these three factors must be considered, as they may either independently or in combination influence the results. Each of these will be considered separately, since it is impossible to disentangle their combined effects.

7.1 Effect of dialysis on the exercise response

7.1.1 Introduction

No study that I can find has been devoted to the specific effect of dialysis itself on the exercise test, when the patient is studied before and after the procedure. However, numerous studies have been done on the haemodynamic changes seen at rest pre- and postdialysis. The results obtained depend on the degree of circulatory volume overload at the time of testing. Del Greco et al. (1969) showed that after dialysis there was an increase in cardiac output (C.O.) and a decrease in calculated total peripheral resistance (T.P.R.) in some of those who had frank circulatory overload prior to dialysis, while those without prior congestion had a slight fall in C.O. with a small rise in T.P.R. Goss et al. looking at a more homogeneous group of patients without clinical overload, found a raised C.O. (mean haemoglobin of the group 6,4 gm/100 ml), and a raised mean arterial pressure (M.A.P.) and T.P.R. before dialysis. After a mean weight loss of 1,7 kg and a decrease in blood volume, there was a fall in C.O. but a rise in M.A.P. and T.P.R. Goss related these changes to

a reduction in central blood volume and possibly to the rise that occurs in pH postdialysis. Hensel (1973 b) found in 10 patients that in spite of a weight loss of 1 kg , there was only a marginal change in total blood volume and cardiac output. However, in spite of no significant change in M.A.P., there was a significant rise in T.P.R. Thus it appears that the C.O. falls to a variable degree after dialysis, the actual fall depending on the amount of fluid removed, but more striking is the rise in T.P.R., with or without a rise in M.A.P.

7.1.2 Experience of the effect of dialysis on the exercise response of six patients

Six patients were chosen, four of whom were still in hospital for home training and two of whom were at home. There were five males and one female (S.P.). Table I shows the relevant patient data. Clinical overload was diagnosed on the basis of an elevated jugular venous pressure measured at 45 degrees with or without hepatomegally and peripheral oedema. One patient (K.P.) was receiving thyroxine for suspected myxoedema. The postdialysis test was delayed for eight to 10 hours to allow any possible heparin effect to subside. The mean weight loss was 1,9 kg.

Table II shows the results of the exercise test before and after dialysis. A striking clinical feature was the increase in muscle fatigue experienced after dialysis. The blank spaces indicate that the patient was unable to reach that particular oxygen consumption. Although on paired 't' testing no significant differences were found in the values before and after dialysis, there is a tendency for a greater tachycardia to develop postdialysis on exercise, while the reverse is seen for the minute ventilation. Nonetheless these changes fall within the normal

Table I - Patient Data

Patient	Age	Duration on Dialysis (months)	Clinical Overload	Wt. loss (kg)
A.S.	29	1	+	0,4
S.P.	25	2	0	3,1
G.F.	19	3	0	2,3
K.P.	46	4	+	1,7
R.B.	20	9	+	2,0
P.R.	31	108	0	1,8

Table II - Effect of Dialysis on the Heart Rate and Ventilation

Patient	Time	Resting H.R.	$H.R._{0,75}$	$H.R._{1,0}$	$\dot{V}_{E_{0,75}}$	$\dot{V}_{E_{1,0}}$
A.S.	Pre	Not done	161	-	30	-
	Post	124	162	-	28	-
S.P.	Pre	100	163	-	32	-
	Post	104	-	-	-	-
G.F.	Pre	88	126	146	26	35
	Post	105	141	158	25	34
K.P.	Pre	88	128	-	29	-
	Post	86	131	-	19	-
R.B.	Pre	98	131	149	23	33
	Post	96	132	160	20	28
P.R.	Pre	96	107	117	21	29
	Post	84	103	113	17	25
	Mean Pre	94	131	137	26	32
	I S.D.	6	19	18	4	3
	Mean Post	95	134	144	22	29
	I S.D.	10	21	27	5	5
	P Value	N.S.	N.S.	N.S.	N.S.	N.S.

variability of the test (Chapter 6).

An attempt was made to subject the six patients to the same workload before and after dialysis. As is seen in Table III, this was achieved with the exception of S.P. who postdialysis (labelled with an asterisk) could not reach her previous final workload, and her final oxygen consumption was much lower, thus largely accounting for the mean difference between the final oxygen consumption levels. Of greater interest is the behaviour of their blood pressure over dialysis and on exercise. As expected with a weight loss of 1,9 kg there is an appreciable drop of blood pressure at rest after dialysis, but at equivalent final workloads there is a negligible difference in the blood pressure readings and what difference there is may be accounted for by S.P.'s results. The steeper rise in the blood pressure postdialysis suggests either excessive spasm or some intrinsic abnormality of the peripheral vasculature not related to volume overload. No detailed haemodynamic studies were done, but if it is assumed that the cardiac output drops or stays the same, then the calculated postdialysis T.P.R. would become higher than the predialysis value at peak exercise showing that the vessels are unable to maximally vasodilate.

7.1.3 Conclusions

From the small number of patients tested, it appears that the alterations in body volume, electrolyte composition and pH that occur over dialysis may produce changes in the circulatory and ventilatory response to exercise, apart from a real increase in subjective fatigue. Thus all future patients to be included in the various select groups, have been tested either midway between dialysis or predialysis, but not the day after dialysis.

Table III - Effect of Dialysis on Oxygen Consumption and Blood Pressure

Patient	Time	Final Workload (Watts)	Final $\dot{V}_{O_2}$ (ml/min)	BP at Rest	Peak Exercise BP
A.S.	Pre	60	991	170/114	210/100
	Post	60	970	140/100	200/100
S.P.	Pre	50	800	140/75	172/75
	Post+	40	470	130/78	160/70
G.F.	Pre	75	1294	140/100	184/75
	Post	75	1340	122/90	182/78
K.P.	Pre	60	982	180/110	246/106
	Post	60	953	156/90	258/114
R.B.	Pre	75	1377	160/55	160/60
	Post	75	1253	130/70	172/30
P.R.	Pre	90	1858	138/95	185/80
	Post	90	1777	115/80	165/75
	Mean Pre		1217	155/92	193/83
	Mean Post		1127	132/85	190/78

7.2 The effect of the arteriovenous fistula

7.2.1 Introduction

Long before the introduction of artificial arteriovenous (A.V.) fistulae for dialysis purposes, the haemodynamic effects of peripheral congenital and acquired fistulae were known. In general (Guyton et al., 1973), at rest large fistulae cause tachycardia, increased cardiac output, increased myocardial contractility, increased total blood volume, and a decreased mean arterial pressure and total peripheral resistance. Bishop et al. (1955) studied three patients with fistulae on exercise in the recumbent position and while confirming the accepted hyperkinetic circulation, suggested that it was principally due to an elevated stroke volume and not to disproportionate tachycardia.

Numerous haemodynamic studies have been done on the effect of artificial A.V. fistulae in haemodialysis patients and these are well reviewed by Bell and Calman (1974). As may be predicted, the largest fistulae produced the most striking haemodynamic changes and some patients were actually pushed into heart failure. Since surgeons have laid down more rigid criteria for the size of the A.V. communication, the incidence of overt heart failure due to the fistula itself has fallen. Nonetheless, most haemodynamic studies at rest still show that the fistula contributes significantly to the overall cardiac output. Only two good studies have been done on the effect of fistula occlusion on exercise. Payne et al. (1972) found that fistula occlusion produced no significant difference in the resting haemodynamic measurements, but during peak recumbent exercise the patients demonstrated a small but significant increase in cardiac output when the A.V. fistula was open. However, this increase was associated

with little difference in heart rate and a drop in stroke volume, so one wonders if the cardiac output estimates on peak exercise, which are notoriously difficult to perform, were correct. Their overall impression, though, was that the fistula produces little haemodynamic deterioration. Dotremont et al. (1970) showed that there was a significant slowing of the heart rate and drop in cardiac output with occlusion at rest. Occlusion on exercise produced a small drop in cardiac output in three of the four patients, but their final conclusion was that moderate supine exercise was not accompanied by a marked increase in the blood flow through the fistula.

7.2.2 Experience with fistula occlusion at rest and on exercise

The simplest way to document the effect of temporary fistula occlusion is to note any change in heart rate. Occlusion of a large fistula causes bradycardia. This response depends on intact baroreceptor reflexes and hence I have compared two groups of patients, those with relatively normal autonomic nervous system responses (see Section 3 of this chapter), and those with an abnormal Valsalva response and/or decreased ankle reflexes. This reliance on the heart rate response assumes that tachycardia is an integral part of the hyperkinetic circulation. However, Moser et al. (1975) tested the effect of fistula occlusion in the recumbent position in 18 patients and found that the deceased cardiac output was due to decreased stroke volume and not heart rate. This was also the opinion of Bishop et al.(1955) testing non-dialysis fistulae in the recumbent position.

The method of testing was initially to occlude the fistula with the patient lying at rest by digital pressure for 10 to 15 seconds and to note

any change in the heart rate from the control value on a Devises Instantaneous Heart Rate Meter connected to a Minograph 800 Recorder. Preliminary testing showed that there was no reflex slowing due to pain. The same procedure was followed during each workload of the exercise test, the occlusion being performed during the second minute of the workload . Table IV shows a mixed group of males and females whose ages ranged from 19 to 41 years. They have been divided into two groups on the basis of the integrity of their Valsalva response and the presence of normal ankle reflexes. Note that the effect of fistula occlusion was tested both lying and sitting at rest on the bicycle to eliminate any effect of posture. At rest in both groups, and sitting merely overcoming the inertia of the bicycle in group A, there is a significant bradycardia with fistula occlusion. This indicates that the fistula is contributing to the resting cardiac output. On mild exertion with elevation of the heart rate and cardiac output the slowing disappeared, and so consistent was this observation that the results at peak workload only have been presented.

7.2.3 Conclusions

At rest when the cardiac output is relatively small, the arteriovenous fistula is responsible for significant shunting. However, on exercise when there is a variable increase in cardiac output the flow through the fistula as a percentage of the total becomes smaller and for practical purposes can be ignored.

7.3 The role of the autonomic nervous system on the exercise response

7.3.1 Introduction

A number of workers have studied the autonomic nervous system in patients with chronic renal failure and patients on haemodialysis. The

Table IV - Effect of Fistula Occlusion on Heart Rate Response at Rest and During Exercise

	H.R. Recumbent		H.R. at 0 Watts		H.R. on Peak Exercise	
	Open	Closed	Open	Closed	Open	Closed
A. In those with a normal baroreceptor response and normal ankle reflexes						
Mean	85,6	79,6	97,8	93,6	149,6	150
I S.D.	12,6	15	12,7	11,7	21	23,8
P Value	0,05 - 0,01		0,02		N.S.	
Number	9		9		9	
B. In those with an abnormal Valsalva and/or decreased ankle reflexes						
Mean	83,0	76,7	86,0	84,3	140	141
I S.D.	10,3	6,7	8,2	6,6	22,3	25,4
P Value	0,05 - 0,01		N.S.		N.S.	
Number	6		6		6	

consensus of opinion is that there is some disturbance and that this may be related to the more common entity of uraemic peripheral neuropathy. However, exactly how this disturbance relates to the cardiovascular reflexes and to what extent healthy dialysis patients are affected is uncertain. The response to the Valsalva manoeuvre and passive tilting was found by Hampers et al. (1967) to be abnormal in patients undergoing bilateral nephrectomy, but Dotremont et al. (1970) demonstrated a normal Valsalva response in a healthier group. It is well known that the Valsalva response may become temporarily abnormal during cardiac failure in non-renal patients, while Mostert et al. (1970) showed the same relationship to circulatory volume overload in patients with chronic renal failure. Thus, in assessing the Valsalva response, consideration must be given not only to the integrity of the autonomic nervous system, but also to the circulatory volume of the patient. Lowenthal and Reidenberg (1972) found that uraemics had a higher resting heart rate, but that there was a flat dose response curve to atropine, suggesting either that vagal function is impaired or that the cardiac pacemaker cells have a decreased sensitivity to acetylcholine. Pickering et al. (1972) tested the baroreceptors in 32 haemodialysis patients by relating the reflex slowing of the heart to an arterial pressure rise induced by injection of phenylephrine. They found that baroreflex sensitivity was less in the older patients and in those with higher blood pressures and concluded that there may be actual resetting as postulated by McCubbin et al. (1956). This postulate suggests that when the factors producing the hypertension are removed the hypertension may persist because the baroreceptors have become accustomed to the higher pressure and thus inappropriately maintain its elevation. Lazarus et al. (1973) on the other hand extending the work originally published by Hampers et al. in 1967, confirmed that there was

an abnormal baroreceptor response to phenylephrine injections, but concluded that this was due to blunting and not actual resetting, possibly as a result of thickened vessels and hence decreased sensitivity. Jirka and David (1973) studied the baroreceptor response to angiotensin infusion in subjects with chronic renal failure (only one was on dialysis),some of whom were hypertensive and others normotensive, and concluded that there was no change in baroreceptor activity, but that there was the expected age-related decline in sensitivity. Kersh et al. (1974) studied an unusual group of patients who developed hypotension on dialysis and found evidence of autonomic neuropathy in six of the eight. They found a correlation between the abnormal baroreceptor responses and evidence of peripheral neuropathy and concluded that both defects were part of the generalized neuropathy seen in the uraemic state. Ewing and Winney (1975) studied the response of 26 patients on haemodialysis to the Valsalva manoeuvre and sustained handgrip. Half the patients had an abnormal Valsalva and an abnormal handgrip. None of the patients were on antihypertensive therapy and none had clinical evidence of peripheral neuropathy or autonomic neuropathy. They concluded that autonomic nerve fibres may be damaged in the absence of symptoms of autonomic neuropathy and unrelated to age or the resting heart rate. In many of the above papers little emphasis is placed on the age, blood pressure and volume status of the patients and as is clear, each of these factors is of great importance in any study of the cardiovascular reflexes.

7.3.2 Experience with cardiovascular reflexes in dialysis patients

The tests for autonomic disturbance in the dialysis patients were only performed at rest and were chosen for their simplicity and ease of performance. The tests were the heart rate response to mental arithmetic,

the heart rate and blood pressure response to two minutes vertical tilting and the heart rate response to the Valsalva manoeuvre. Apart from Phase 4 of the Valsalva, where there is reflex vagal bradycardia due to elevation of the blood pressure, these procedures test the integrity of the sympathetic nervous system. The normal heart rate response to the Valsalva is obviously the converse of the blood pressure response with an overshoot tachycardia after the release of the intrathoracic pressure (Phase 3) followed by reflex vagal bradycardia (Phase 4). The heart rate response to the Valsalva has been investigated by Elisberg (1963) and Levin (1966). The heart rate was recorded by a Devices Instantaneous Heart Rate Meter and for each test there was an initial control period. The fastest heart rate over a 10 second period was taken for the response to mental arithmetic, while the heart rate at the end of the two minute tilt period was taken in all cases, as was the blood pressure. The Valsalva was performed sitting and, with a noseclip, the subject was required to maintain an intrathoracic pressure of between 40 and 50 mm Hg for 15 seconds. The percentage change from control is measured for the peak overshoot (Phase 3) and the bradycardia (Phase 4), as well as the Levin Valsalva ratio, i.e. $\frac{\text{maximal tachycardia (beats/min)}}{\text{maximal bradycardia (beats/min)}}$. The Valsalva was repeated two or three times and the best response taken.

Although normal values have been quoted for each of these tests in the literature (Elisberg, 1963; Levin, 1966; Frohlich et al., 1967), because of variability and differences of standardization, I used my own controls, who were young male hospital personnel. Four of these controls also acted as controls for the exercise test. From the pool of 40 dialysis patients tested, three groups were selected on the basis of age and evidence of peripheral neuropathy, diagnosed purely on clinical

grounds. The groups included both sexes and no patient was on antihypertensive therapy at the time of testing.

Table V gives a breakdown of the results in the control and patient groups. Results are given as a mean and a range; no statistics are included because of the wide scatter. The Valsalva figures are expressed as the percentage change (Δ) from control to Phase 3 (Peak) and from control to Phase 4 (Trough) and as a ratio. The overriding impression is the tremendous variability of the results, both in the control and the patient groups. In spite of this and the small number of subjects, a few general points may be made about each test. Firstly, with regard to the Valsalva there appears in the patient groups to be a decline in responsiveness with increasing age and the difference between Groups 2 and 3 may be one of age and not the presence of clinical neuropathy. Similarly, the fall off in the response to mental arithmetic may be age-related, although the basal heart rates of the patient groups are much the same. However, only three of the five Older Group patients were tested for their response to arithmetic and tilting. There is no real difference between the heart rate response to tilting of any of the four groups. The basal blood pressure of the patient groups is definitely higher than the controls, but each group responds to the tilt with a minor fall in systolic blood pressure and with the exception of Group 3 a small drop in diastolic pressure. Within the patient groups there were a number of individuals who had an exaggerated hypotensive response, but this could usually be explained by volume depletion, although care was taken not to test any patient on the day after dialysis.

In Table VI the patients are rearranged into a younger group (< 30 years) and an older group (> 30 years) and compared again to the

Table V - Cardiovascular Reflexes in Control and Patient Groups

	Age	Valsalva			Arithmetic		Tilt			
		% Δ Peak	% Δ Trough	Ratio	Basal	Test	Basal	Test	BP Supine	BP Erect
1. Controls n = 12										
Mean	29	+ 48	-22	1,92	70	88	68	85	120/70	112/81
Range	19-35	17-71	9-37	1,52-2,45	60-84	60-90	60-78	60-120	SBP 104-138 DBP 58-82	SBP 95-140 DBP 74-90
2. Young Group. No Neuropathy n= 10										
Mean	27	+ 40	-16	1,69	84	98	84	98	138/88	134/86
Range	19-35	25-83	5-36	1,33-2,09	57-108	72-138	66-102	72-114	SBP 105-160 DBP 74-105	SBP 90-165 DBP 45-115
3. Young Group. Clinical Neuropathy n= 6										
Mean	35	+ 34	-15	1,58	86	98	81	96	140/85	130/92
Range	30-39	13-54	4-33	1,31-1,88	66-96	78-114	66-96	84-114	SBP 120-160 DBP 65-110	SBP 102-145 DBP 83-105
4. Older Group. n = 5										
Mean	47	+ 22	-5	1,29	87	95	90	108	133/80	131/78
Range	41-51	5-31	0-10	1,05-1,47	78-96	87-108	84-96	96-132	SBP 130-140 DBP 75-82	SBP 115-140 DBP 74-80

Table IV - Valsalva Ratio in Controls, Younger Patients and Older Patients

1. Controls	Age	Supine BP	Ratio	2.Young Group	Age	Supine BP	Ratio	3.Older Group	Age	Supine BP	Ratio
M.P.	35	114/80	1,85	D.C.	25	160/103	1,57	D.P.	35	146/96	1,39
P.H.	32	122/72	1,75	G.F.	19	140/105	2,09	A.P.	35	120/76	1,55
J.E.	34	124/68	2,1	B.B.	19	150/88	1,95	P.R.	32	145/95	1,61
J.M.	34	-	1,52	M.B.	25	132/74	1,76	O,J.	35	160/90	1,96
D.M.	30	130/82	2,32	R.B.	20	115/75	1,69	K.E.	30	120/85	1,31
D.R.	30	110/75	2,15	S.P.	25	105/75	1,33	A.D.	39	142/90	1,46
W.H.	24	112/62	2,45	A.S.	29	160/110	1,37	A.G.	32	135/65	1,59
K.M.	25	104/70	1,66					I.C.	34	120/90	1,88
D.L.	19	115/58	1,92					L.O.	31	140/88	1,86
H.P.	25	122/73	1,96					E.M.	44	140/80	1,40
P.T.	27	130/69	1,74					R.C.	41	130/82	1,05
S.K.	26	138/80	1,58					S.D.	50	161/99	1,47
								J.A.	49	130/82	1,32
								L.M.	51	140/75	1,22
Mean	29	120/70	1,92		23	137/90	1,6		38	138/85	1,51
Range		SBP104-138 DBP58-82	1,52-2,45		19-29	SBP 105-160 DBP 74-110	1,33-2,09		30-51	SBP 120-161 DBP 65-99	1,05-1,96
n = 12				n = 7				n = 14			

control group with respect to their supine blood pressures and the Valsalva ratio devised by Levin (1966). Within the control group there is no difference in the ratio between those under and those over 30 years. In both the patient groups the supine blood pressure is consistently higher than in the control group and it is possible that this higher pressure, perhaps together with the age-related effect shown in Table V and possibly confirmed here (Young group ratio 1,60 vs. Older group ratio 1,51), could be stimulating the baroreflex to produce an appropriate diminution in the maximum tachycardia (Phase 3) and hence a lesser maximum bradycardia (Phase 4).

Not shown here, but hinted at in subsequent chapters and given statistical respectability in Chapter 14, is an inverse relationship between the rate of rise of systolic blood pressure and the increase in heart rate during exercise. This strong inverse relationship (the higher the systolic pressure the lesser the exercise tachycardia) suggests that during exercise the patients' baroreceptors are functioning reasonably normally.

7.3.3 Conclusions

This small study in a group of healthier patients has done little to dispel the confusion surrounding the subject. It does support the suggestion that increasing age, as in the normal population, results in blunting of the Valsalva response but in the patient group the age-related changes are seen much earlier, and there is also the suggestion that relatively minor degrees of hypertension *per se* may cause an appropriate blunting via the baroreceptors of the Valsalva ratio. The heart rate and blood pressure response to tilting and the heart rate response to mental arithmetic do not appear grossly abnormal, with the exception of a few patients with postural hypotension. Also evidence of peripheral neuropathy does not necessarily imply involvement of the autonomic nervous system.

Finally, it is impossible to generalize from these results at rest to the effect the autonomic nervous system may have on the exercise response. However, subsequent chapters will show that an inverse relationship between blood pressure and heart rate is preserved during exercise, and thus whatever blunting there may be at rest, gross abnormalities of the autonomic nervous system are unlikely to account for the peculiar exercise responses of the dialysis patients.

CHAPTER 8

THE EXERCISE RESPONSE OF A SELECT GROUP OF PATIENTS AND MATCHED CONTROLS

The main object of the Thesis is to study the response to standardized exercise of a healthy group of rehabilitated patients. Forty patients were tested on at least one occasion, and from this pool the results of 12 young males have been selected for presentation. Selection was made on the basis of age (under 40 years), sex (all males) and resting blood pressure (under 160/105 mm Hg) and no patient who fulfilled these criteria was excluded. The patients were basically fit, were fully or partially rehabilitated, and were initially chosen to represent a wide range of duration on dialysis. As previously mentioned, each patient was carefully examined, looking particularly for evidence of circulatory overload and lung disease, and for evidence of abnormal cardiovascular reflexes or an abnormally large arteriovenous fistula. Only patients who were not on routine cardiovascular drugs were accepted - one patient, D.C., had been on antihypertensive treatment but his drugs were stopped two weeks before the test. The resting blood pressure cut off decided on was 160/105 because those with pressures above this level were on antihypertensive drugs. Routine blood tests, a resting ECG and a single inspiratory chest film were done. Patients were only tested between dialysis or predialysis, and not the day after. The methods for examining the effect of the fistula and the cardiovascular reflexes were discussed in Chapter 7, while the routine methods of bloodless exercise testing were fully covered in Chapter 4.

Because exercise tests vary from laboratory to laboratory, it was important to have our own controls, who would be representative of a sedentary group and not an athletic one. In addition, because of the

known variation in exercise response induced by age, sex and differing body dimensions, it was important that the control group be carefully matched against the test group. Accordingly, from a pool of 24 controls tested, 12 healthy young males were selected. The controls were not generally examined apart from blood pressure and heart rate measurements, nor were any special investigations performed. Half of the controls were tested some months before the patients, and the remainder over the same time interval as the patients.

Because all the dialysis patients selected for presentation were anaemic, it was important to compare them not only to matched normal subjects but also to matched anaemic patients who had no evidence of underlying renal disease. Thus anaemic controls were assiduously looked for, but only two patients in this age group could be found, one with aplastic anaemia and short stature and another recovering from a sickling crisis. It was felt two patients would not be representative of compensated non-renal anaemics and thus the information on this group is taken from the literature (see Chapter 2, Section 2 and Chapter 10, Section 4). Clearly the absence of my own anaemic controls is a regrettable hiatus.

8.1 Background data on the patients and controls

Table 1 shows the initials, age, diagnosis, time of testing in relation to the next dialysis, duration on dialysis and degree of rehabilitation of the 12 males. Their mean age was 29,7 years (range 20-39 years) and mean duration on dialysis 3,3 years (range 0,15 - 9,5 years). The majority had established or presumed chronic glomerulonephritis (CGN), one chronic pyelonephritis (CPN) and two different forms of congenital renal disease. Ten of the 12 patients were fully rehabilitated and 10 of the 12 were tested on a day in between dialysis.

Table I - Patient Data

Patient	Age	Diagnosis	Time of Testing	Duration Dialysis (years)	Rehabilitation
R.B.	20	CPN	Inter	1,1	Full
K.E.	30	CGN	Inter	4,5	Full
G.D	35	? CGN	Inter	0,45	Partial
P.R.	32	Megacystus	Pre	9,5	Full
A.P.	35	CGN	Inter	5,0	Full
B.B.	21	CGN	Inter	0,15	Partial
M.B.	25	? CGN	Inter	2,75	Full
G.F.	20	CGN	Pre	0,7	Full
D.P.	36	CGN	Inter	5,45	Full
H.D.	34	Congenital	Inter	2,0	Full
A.D.	39	? CGN	Inter	8,5	Full
D.C.	25	CGN	Inter	0,5	Full

Table II gives further patient data. The resting blood pressure is a mean of the lying, sitting and standing, and the resting heart rate is similarly a mean of at least three recumbent measurements. The mean blood pressure of the group is 137/88 with a systolic range of 113 to 152 and a diastolic range of 60 to 108, and the mean heart rate 84 with a range of 73 to 96, neither of which would alert the clinician to the abnormal results which will be shown for the exercise test. The mean haemoglobin was 8,5 gm/100 ml (range 5,7 - 10,3) and the mean cardiothoracic ratio 45 per cent (range 37 - 51). None of the patients were anephric and,

TABLE II - Further Patient Data

Patient	Resting BP	Resting H.R.	Clinical Overload	Hb (gm/100 ml)	Serum Creat. (mg/100 ml)	24 hour urine volume (ml)	C.T.R. %
R.B.	113/60	85	±	5,7	16,0	600	48
K.E.	117/80	91	0	9,7	11,6	100	37
G.D.	129/76	78	0	6,9	11,8	200	50
P.R.	141/86	79	0	9,1	13,7	5	42
A.P.	113/71	71	0	10,3	12,4	500	50
B.B.	149/108	85	0	7,8	10,9	200	36
M.B.	133/75	96	0	8,5	10,6	<1000	41
G.F.	146/105	73	0	8,3	>15,0	200	39
D.P.	152/95	84	0	8,8	10,2	500	51
H.D.	153/105	87	0	9,3	13,7	350	43
A.D.	142/98	87	0	9,5	10,9	0	51
D.C.	150/102	96	0	8,0	13,4	400	47

although 10 of the 12 passed some urine (the actual volume being based on their own estimation and not measured), the poor urinary output together with the serum creatinine levels, suggests that their residual renal function was negligible. Only one patient had a possibly elevated jugular venous pressure at 45 degrees.

Table III shows the effect of fistula compression in 11 members of the select group; one patient had a shunt. The results are laid out as in Chapter 7, and show a significant effect of occlusion at rest ($p < 0,001$), but this effect disappears entirely with exercise. In fact at peak exercise the heart rate is faster with the fistula closed than when open.

Table IV gives the results of the cardiac reflexes in this particular group and they are compared to the same controls used in Chapter 7. Four of these controls acted as controls for the exercise test as well. The comparison between the two groups is now more valid, since the groups are both male and the mean age is the same. Only two patients, K.E. and A.D., had evidence of clinical neuropathy. The same tentative conclusions and reservations again apply.

Finally in this section on patient data, Table V gives the comparative data for the control and select patient groups. This data is of great importance, since significant differences in age, height, weight or basic lung function could account for differences in the exercise response. However, as is seen, the two groups are very well matched and the greatest statistical difference between any parameter was for the comparative weights ($p = 0,2 - 0,3$).

8.2 Exercise results in the patients and controls

It is important to note that nine of the 12 select males had at

Table III - Effect of Fistula Occlusion on Heart Rate in Eleven Select Male Patients

	H.R. Recumbent		H.R. 0 Watts		H.R. Peak Exercise	
	Open	Closed	Open	Closed	Open	Closed
Mean	85,5	78,3	96,6	93,6	157,4	159,6
± I S.D.	9,9	10,7	12,5	11	14,9	16,4
P Value	< 0,001		0,1 - 0,2		0,1 - 0,2	

Table IV - Autonomic Nervous System - Heart Rate and Blood Pressure Responses

Group	Age	Valsalva			Arithmetic		Tilt			
		%Δ Peak	%Δ Trough	Ratio	Basal	Test	Basal	Test	BP Supine	BP Erect
1.Controls n = 12										
Mean	29	+ 48	-22	1,92	70	88	68	85	120/70	112/81
Range	19-35	17-71	9-37	1,52-2,45	60-84	60-90	60-78	60-120	SBP 104-138 DBP 58- 82	SBP 95-140 DBP 74- 90
2.Select dialysis n = 11										
Mean	29,7	+ 31	-18	1,61	86	98	81	100	138/87	132/89
Range	20-39	1-49	5-36	1,22-2,11	72-108	72-114	66-108	84-126	SBP 115-160 DBP 65-105	SBP 115-165 DBP 60-115

Table V - Controls and Patients

Subjects	Age	Height (cms)	Weight (kg)	BSA	FEV_1/FVC Ratio
1. Controls					
n = 12					
Mean	28,8	174,8	66,1	1,80	78,1
Range	19 - 37	168 - 184,5	55,2 - 81	1,66-2,04	61 - 89
2. Patients					
n = 12					
Mean	29,7	173,3	70,8	1,84	79
Range	20 - 39	162,5 -182	57,4 - 87,5	1,6-2,06	68 - 88

least one repeat exercise test performed, and in the case of R.B., as many as four. Seven of the 12 subjects had cardiac output studies done and two had repeat cardiac outputs. The figures presented here are those obtained at the time of their final repeat exercise test or at the time of the first cardiac output study, so that there is continuity between this chapter and the later chapters on the more detailed haemodynamics. In order to facilitate understanding of the data, it is presented both in table and scattergram form. The statistics are based on an unpaired Students 't' test accepting significance at the five per cent level. The respiratory parameters of the two groups will be dealt with in a separate chapter (Chapter 11), and here only the non-invasive haemodynamic results will be discussed.

In Table VI and Figure 1 are presented the final workload and oxygen consumption ($\dot{V}_{O_2}$) achieved by the two groups and the calculated respiratory quotient (RQ) during the peak work period. Although in all cases the test was submaximal, it is clear from the patients' peak RQ that even at their significantly lower workload and $\dot{V}_{O_2}$ they were in fact exerting themselves more than the controls. Corroborative evidence for this will be presented later when the patients' arterial lactate levels are discussed. The mechanical efficiency for each subject has been calculated at a workload of 50 Watts and expressed as the $\dot{V}_{O_2}$ in ml/min at that level. There was no significant difference in the efficiency of the two groups, and hence this is not the reason for their strikingly different work performance.

Table VI - Work Performance of the Patients and the Controls

Group	Final $\dot{V}_{O_2}$ (ml/min)	Final Workload (Watts)	Peak RQ	$\dot{V}_{O_2}$ at 50W (ml/min)
1. Controls				
n = 12				
Mean	1973	123,8	0,948	994
I S.D.	259	10,0	0,05	110
2. Patients				
n = 12				
Mean	1508	85,4	1,011	1017
I S.D.	240	13,2	0,083	76,5
P value	< 0,001	< 0,001	< 0,05	N.S.

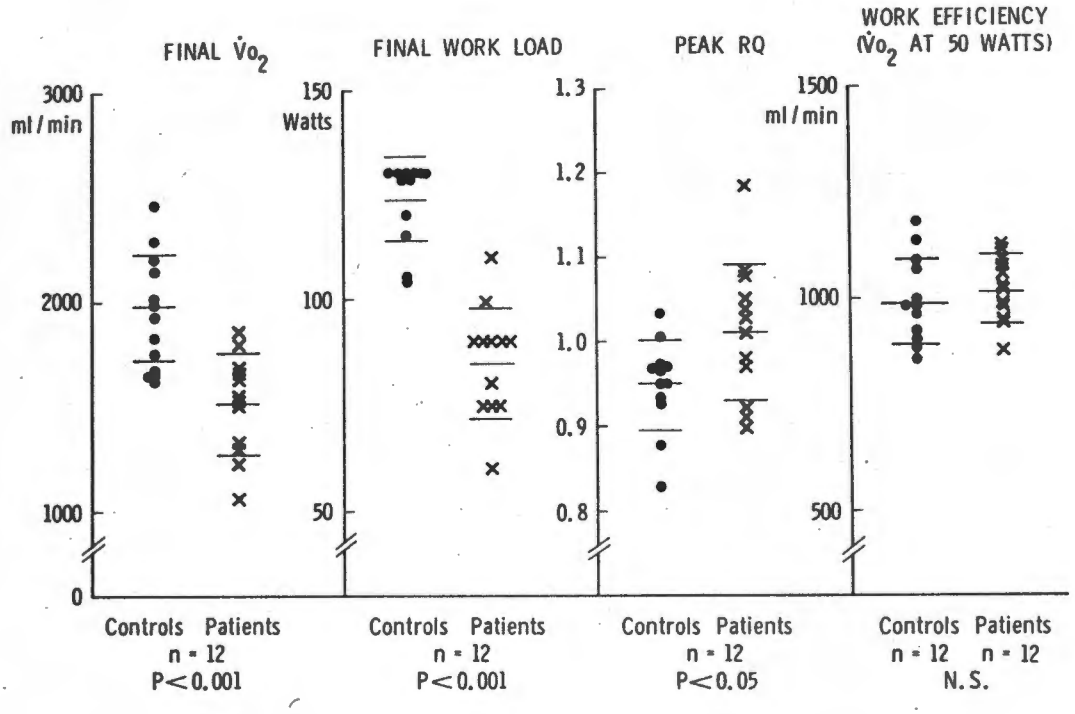

Figure 1 - Work Performance (Mean ± 1 S.D.)

The heart rate achieved at three levels of oxygen consumption is shown in Table VII and Figure 2. Although the mean recumbent heart rate of the patients (84 beats per min) is higher than would be expected for the controls (a recumbent heart rate of control group used for investigating the cardiac reflexes was 68-70 beats/min), this disproportionate tachycardia is maintained throughout exercise. In spite of the significant difference in the mean levels, it is obvious from the scattergram that about half the patients, and this is particularly noteworthy at $\dot{V}_{O_2}$ 1,5 where only eight of the 12 managed this level, developed a pulse rate which fell within the normal range. Part of the explanation is that some patients were fitter than others, but also a number of these developed alarming systolic hypertension during exercise and this blood pressure rise may have reflexly

Table VII - Heart Rate and Predicted Maximum Oxygen Consumption of the Two Groups

Group	H.R./$\dot{V}_{O_2}$ 0,75	H.R./$\dot{V}_{O_2}$ 1,0	H.R./$\dot{V}_{O_2}$ 1,5	Pred.$\dot{V}_{O_2}$ Max. (ml/min)
1. Controls				
n = 12				
Mean	102,3	114,6	139,4	2640
I S.D.	8,6	9,0	12,1	510
2. Patients				
n = 12				
Mean	114	130,8	153,1	1993
I S.D.	10,3	13,3	13,5	413
P value	< 0,01	< 0,005	0,05 - 0,025	< 0,005

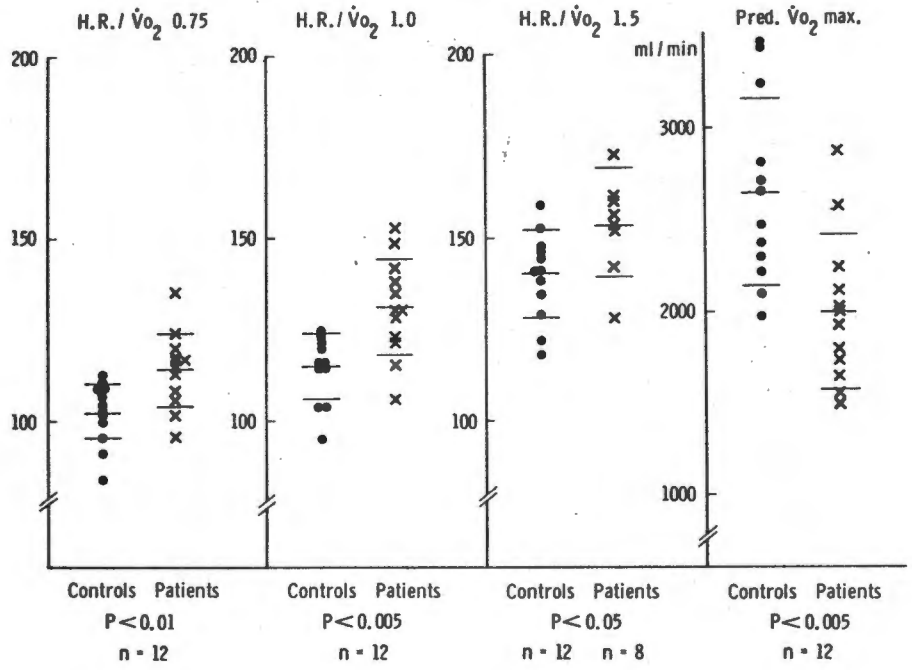

Figure 2 - Heart Rate and Predicted Maximum Oxygen Consumption
(Mean $\pm$ I S.D.)

depressed their expected heart rate. The predicted maximum oxygen consumption was calculated by extrapolating the oxygen consumption/heart rate regression equation to the maximal predicted heart rate, obtained by Åstrands' formula. Within the 10 per cent error inherent in any calculation of maximal oxygen consumption, the prediction for the control group illustrates that they were by no means outstandingly fit. Although the mean of the patients is significantly lower than the controls, there is a wide scatter and again some fall well within the control range. It is difficult to know what these predictions mean when some patients develop hypertension and presumed reflex slowing during exercise. This may be the explanation for the observation of Mallie et al. (1974) that dialysis patients reach their

maximal oxygen consumption at submaximal heart rates.

Figure 3 is a graph modified from one of J.E. Cotes (personal communication)to illustrate what various levels of oxygen consumption mean in terms of everyday activity. The mean patient final $\dot{V}_{O_2}$ was the equivalent of hard work for young men, whereas the control equivalent was playing squash. It is informative to realize that the patients are developing significantly greater tachycardia at the level of washing or walking at a medium pace ($\dot{V}_{O_2}$ 0,75 - 1,0). Thus this tachycardia occurs during everyday life and is not a phenomenon restricted to the laboratory.

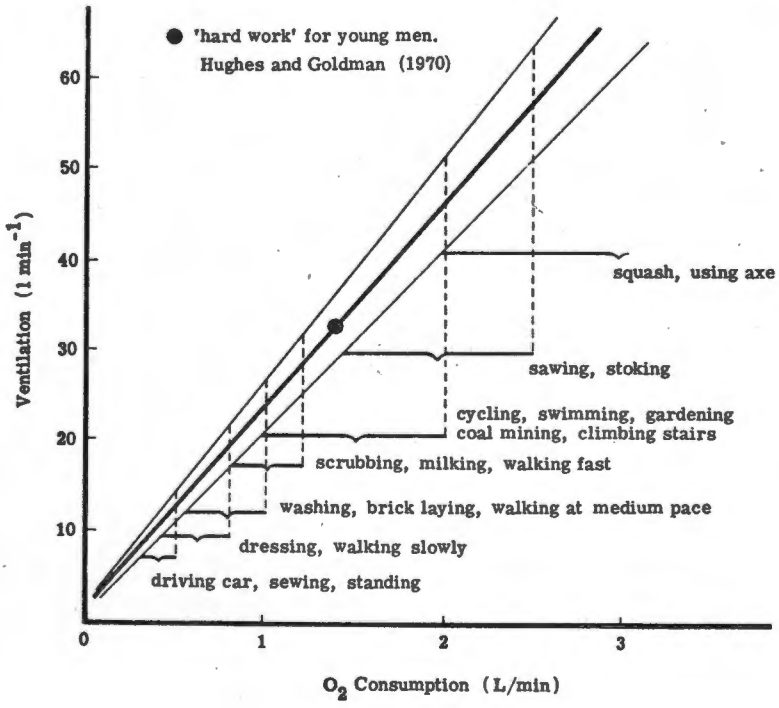

Figure 3 - Human Energy Expenditure and Ventilation During Selected Tasks

8.3 The response of the blood pressure on exercise in the two groups

The reproducibility and reliability of sphygmomanometer blood pressure recordings was discussed in Chapter 6. Here I want only to present the blood pressure data in the control group and the 12 select patients. Only seven of the 12 controls had blood pressure measurements during exercise. The mean age of these seven controls was 29 years with a range of 24 to 37 years, and the mean of a single pressure taken merely sitting on the bicycle was 108/67 with a systolic range of 95 to 115 mm Hg and a diastolic range of 65 to 75 mm Hg. Thus their resting pressure was significantly lower than the mean resting pressure of the patients which was 137/88. Clearly in comparing the patient and the control groups attention must be focused not only on resting pressures but also on the rate of change of the pressure during exercise.

In Figure 4 are plotted the actual readings of systolic and diastolic pressure during exercise for the seven controls. The computed regression equation, where Y = pressure and X = oxygen consumption, is shown together with the correlation coefficient in the case of the systolic pressure. The interrupted line shows the mean arterial pressure calculated by adding one third of the pulse pressure to the diastolic pressure. It can be seen that at $\dot{V}_{O_2}$ 1,5, which was the mean level reached by the patients, the mean systolic blood pressure was about 150 mm Hg and the diastolic 67.

When we turn to the response of the patient group, it was clear from the raw data that some of the patients developed an alarming hypertension during exercise, while some remained relatively 'normotensive'. Thus the patients were thereafter divided into two subgroups, which will be called the 'normotensive' and hypertensive subgroups from now on. It so happened that six patients fell into each subgroup. It must be stressed

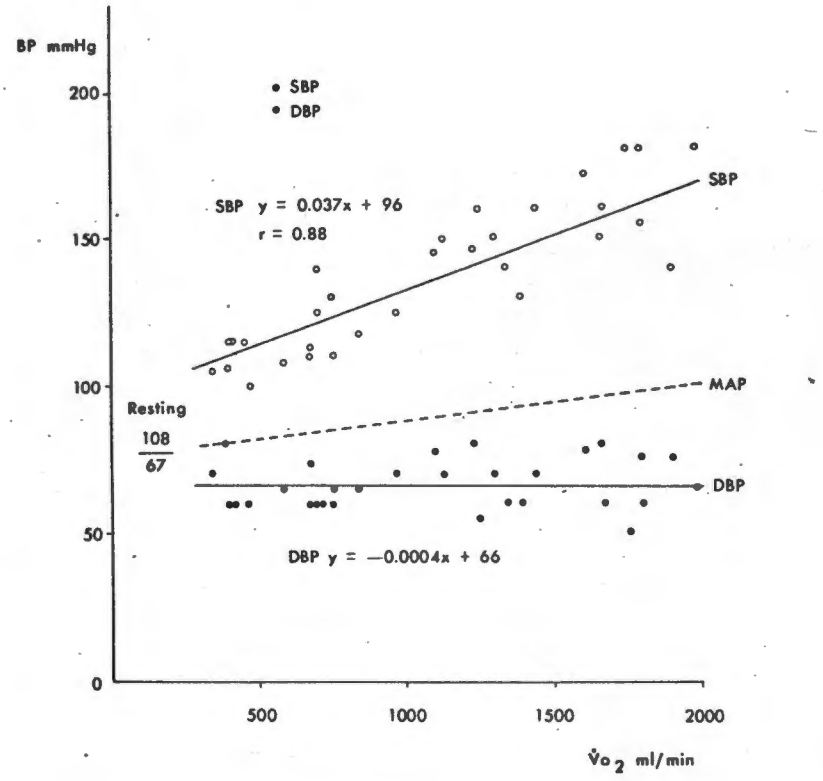

Figure 4 - Blood Pressure Response of Control Group on Exercise (n = 7)

that this subdivision is based on the patient's blood pressure response on exercise, although it will be seen that the 'normotensives' usually, but not invariably, had lower resting pressures as well.

In Figure 5 are shown the results of the 'normotensive' subgroup plotted on the same axes as the controls. The resting pressure of these patients is 128/83 which is lower than that of the group as a whole, but it can be seen that one patient started with a pressure of 155/104, so that the initial pressure alone, although a good guide, is not entirely predictive of the subsequent exercise response. The correlation coefficient (r = 0,72) is not as good as in the controls (r = 0,88), but the systolic pressure at $\dot{V}_{O_2}$ 1,5 is 170 mm Hg which is 20 mm Hg higher than the control

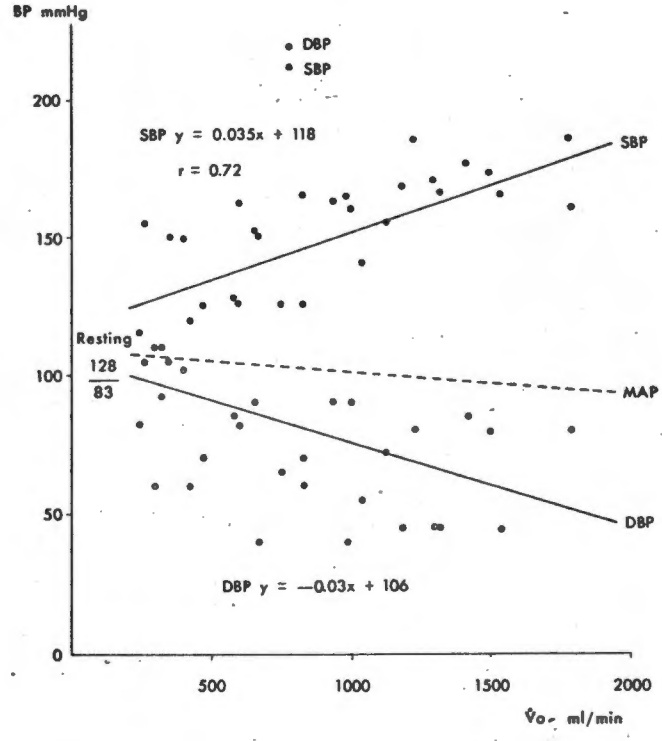

Figure 5 - Blood Pressure Response of 'Normotensive' Subgroup on Exercise (n = 6)

group. However, the most striking difference is in the behaviour of the diastolic pressure, which together with the calculated mean arterial pressure, actually drops on exercise together with a marked widening of the pulse pressure.

In Figure 6 is shown the response of the six patients who fell into the hypertensive subgroup. The mean resting pressure is 148/97, but again there is one patient whose resting pressure was 120/75. Here there is a good correlation coefficient (r = 0,89) for the systolic pressure regression equation, and the systolic pressure at $\dot{V}_{O_2}$ 1,5 is

208 mm Hg. The diastolic pressure falls slightly, but there is now an overall rise in the calculated mean arterial pressure.

It was mentioned earlier that a number of patients had repeat tests performed and provided the body weight and the body volumes remained the same, the blood pressure response was reproducible. Table VIII shows this reproducibility in two patients, one from the 'normotensive' subgroup and the other from the hypertensive. R.B. was restudied after an interval of five months when his weight had changed 0,8 kg and his C.T.R. by two per cent, and G.D. after a month with a weight change of 1,5 kg and C.T.R. of four per cent; the haemoglobin of both these patients was the same on each occasion. As can be seen the reproducibility of both systolic and diastolic pressure is reasonably good.

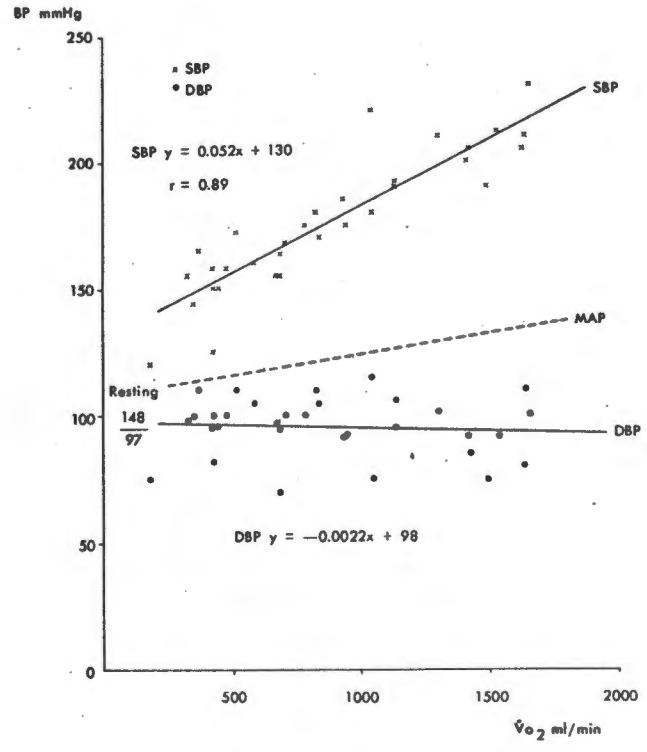

Figure 6 - Blood Pressure Response of Hypertensive Subgroup on Exercise (n = 6)

Table VIII - Reproducibility of Blood Pressure in Two Patients

Workload (Watts)	R.B. - 'Normotensive'				Workload (Watts)	G.D. - Hypertensive			
	SBP		DBP			SBP		DBP	
	(i)	(ii)	(i)	(ii)		(i)	(ii)	(i)	(ii)
0	115	108	45	52	0	135	125	88	82
25	140	120	35	35	25	155	155	85	70
50	150	140	30	20	50	170	180	85	75
75	155	155	30	20	75	200	190	85	75

Figure 7 is a combined graph illustrating the behaviour of the systolic pressure of the controls and the two patient subgroups. The three regression equations are plotted against oxygen consumption as before, but the pressure scale is magnified. There is a significant difference ($p < 0,005$) between the resting levels of blood pressure of all three groups. More important, however, the rate of rise of the systolic pressure in the hypertensive subgroup is significantly (slope $p < 0,025$) different from controls, and almost reaches the five per cent level ($p = 0,1 - 0,05$) when compared to the 'normotensive' subgroup. Thus the difference in the resting levels cannot alone account for the alarming rise in the hypertensive subgroup. In addition, when the diastolic and calculated mean pressures are taken into consideration, there is a fundamental difference in behaviour of the two subgroups, and both subgroups behave abnormally when compared to the controls.

In order to investigate what factors may be responsible for this striking difference in blood pressure behaviour on exercise, the basic patient data has been restructured to represent now the 'normotensive' and hypertensive subgroups and is shown in Table IX. In most regards the two subgroups are comparable and only age and H.R./$\dot{V}_{O_2}$ 1,0 show a significant difference on the Wilcoxon test, suggesting that it is the older group who develop this alarming hypertensive response and that the blood pressure rise may in turn produce a reflex bradycardia. It is possible, if the patient numbers were larger, that duration on dialysis and heart size might also correlate with the hypertensive response. The final mean RQ (not shown) of the 'normotensive' subgroup was 1,051 while that of the hypertensive was 0,971 and it is possible that the 'normotensives' because their metabolism became anaerobic, were actually exerting themselves more than the hypertensives, but if this

were so, then the difference in their pressure response would be even more striking.

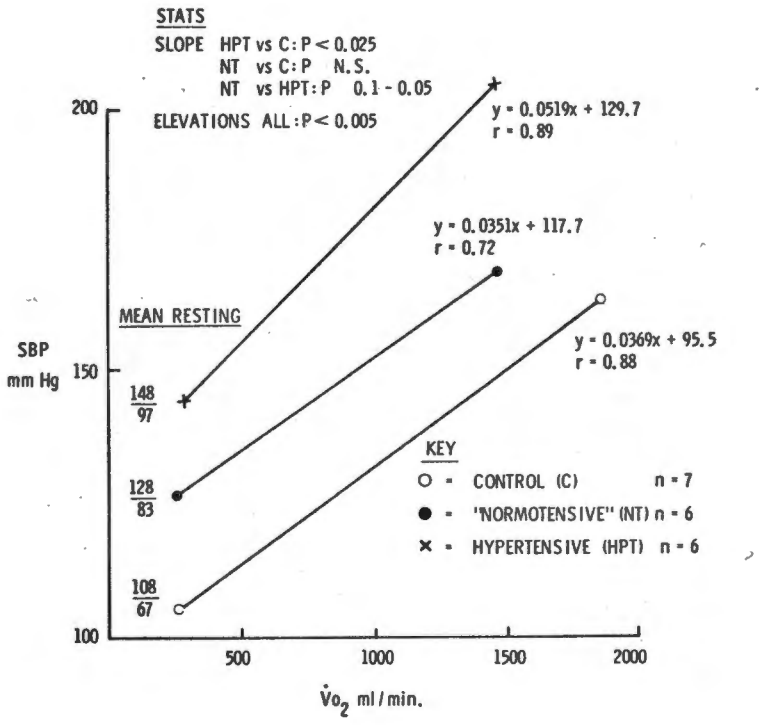

Figure 7 - Systolic Blood Pressure on Exercise

8.4 Discussion

Most authors who have investigated the exercise response of dialysis patients, have not standardized their patients in regard to age, sex, body dimensions, blood pressure, overload and drug therapy, nor have they been compared with matched controls. Charing Cross Hospital organises a charity walk for their patients each year and four of the select group managed between 10 and 15 miles, suggesting that many of them were apparently reasonably fit. Thus, although decreased

Table IX - Patient Data of the 'Normotensive' and Hypertensive Subgroups

Patients	Age	Duration Dialysis (years)	BSA	Hb	C.T.R.	Final $\dot{V}_{O_2}$ (ml/min)	H.R./$\dot{V}_{O_2}$ 1,0
'Normotensive'							
R.B.	20	1,1	1,73	5,7	48	1297	142
K.E.	30	4,5	1,77	9,7	37	1858	130
A.P.	35	5,0	2,06	10,3	50	1787	106
B.B.	21	0,15	1,69	7,8	36	1319	152
M.B.	25	2,75	2,00	8,5	41	1542	138
G.F.	20	0,7	1,60	8,3	39	1232	148
Mean	25	2,4	1,80	8,4	42	1506	136
Range	20-35	0,15-5,0	1,60-2,06	5,7-10,3	36-50	1232-1858	106-152
Hypertensive							
G.D.	35	0,45	2,02	6,9	50	1498	123
P.R.	32	9,5	1,87	9,1	42	1650	115
D.P.	36	5,45	1,74	8,8	51	1543	128
H.D.	34	2,0	1,71	9,3	43	1053	135
A.D.	39	8,5	1,83	9,5	51	1674	122
D.C.	25	0,5	2,00	8,0	47	1643	130
Mean	34	4,4	1,86	8,6	47	1510	126
Range	25-39	0,45-9,5	1,71-2,02	6,9-9,5	42-51	1053-1674	115-135

work performance has been unanimously agreed upon in the literature, the actual physical limitations of this healthy group as revealed by standard exercise testing, came as a surprise. The fact that the decreased work performance was associated with anaerobic metabolism in many patients indicated not only that they were definitely trying, but also that they were much closer to their maximal work capacity than the controls. There is, however, some overlap between the patients and the controls and some patients fell within the control range showing that reasonable rehabilitation can be achieved. More important is that at the relatively low levels of oxygen consumption reached during everyday activity, the patients develop a disproportionate tachycardia and in some cases an alarming hypertension. However, there appears to be two subgroups : those with the alarming blood pressure rise have less tachycardia (H.R./$\dot{V}_{O_2}$ 1,0 = 126 compared to controls 114,6) than the 'normotensive' subgroup (H.R./$\dot{V}_{O_2}$ 1,0 = 136). Because of this blood pressure difference, indirect methods (e.g. Åstrands' Nomogram) for predicting maximal oxygen consumption become even less reliable. Some of the heart rate difference may be due to age alone, as the patients with the slower heart rates are 10 years older than the others, but age alone is unlikely to account for this discrepancy.

Of greater interest, because hardly studied, is the blood pressure response of the patients and the possible factors which cause some patients to respond relatively normally and others to become hypertensive. Although the hypertensive subgroup had a mean resting level of 148/97, this level has previously been acceptable and most units would not have instituted any form of therapy. Nonetheless, the resting level does not always predict the exercise response and while in some the systolic pressure and mean arterial pressure increased disproportionately during

exercise, in others there was an actual drop in calculated mean arterial pressure.

Numerous articles have been devoted to the blood pressure response on exercise in hypertensives without underlying renal disease compared to age matched controls. Studies by Sannerstedt (1966), Amery et al. (1967), Julius et al. (1967), and Bruce et al. (1974) throw some light on the problem, but largely in a negative sense. In general, the rate of rise was in proportion to the resting level and only females showed a disproportionate rise similar to our hypertensive subgroup (Sannerstedt, 1966). It has been well established that as age progresses not only is the resting level higher, but there is in fact a disproportionate rise. However, this is only seen when an 18 to 34 year old group is compared to a 50 to 69 year old group (Amery et al. 1967; Julius et al., 1967). Bruce et al. (1974) found that the average change in systolic pressure from rest to the highest level observed was 62 ± 19 mm Hg in healthy men and 56 ± 24 mm Hg in age matched (mean age 49,3 years) hypertensive men. Thus age is very important in the older groups in determining the rate of rise of the blood pressure, but in the younger hypertensive patients, although the blood pressure is set at a higher level the rate of rise is comparable to controls. It has in addition been observed in testing normal subjects, that those under 25 years may show an actual drop in diastolic pressure on exercise, while the response of older patients is a slight increase. Also of interest in Bruce's study was the fact that his hypertensives developed a lesser tachycardia than did the age-matched controls.

Thus the 10 year age difference between the two dialysis subgroups may partly explain why the 'normotensives' showed a drop in their

diastolic pressure and perhaps partly account for the higher resting level in the hypertensives but not for the disproportionate rise on exercise. The higher resting level *per se* is also unlikely to account for the alarming rise. No really convincing cause of the blood pressure difference has yet been found and this aspect will be pursued in later chapters.

Finally, what is the combined haemodynamic effect of tachycardia and hypertension ? Numerous articles (Sarnoff *et al.*,1958; Kitamura *et al.*, 1972) have shown that heart rate alone or the heart rate systolic blood pressure product correlate directly with myocardial oxygen consumption. Since there may be an inverse relationship between heart rate and systolic pressure in some patients, I have used the product as an index of presumed myocardial oxygen consumption. Figure 8 shows the product at three levels of oxygen consumption. No range , standard deviation or statistics are given because both the heart rate and the pressure, taken from the respective regression equations,each involve a scatter and it would be impossible to assess the combined confidence limits. Within the error of this calculation it is clear that, firstly, the product of the dialysis patients is much higher than controls, and secondly because of the blood pressure rise the hypertensive group fare the worst of all. In Bruce's study (1974) no difference was found between his controls and his hypertensives, because of reflex bradycardia in latter group, but here the effect is compounded by their underlying disproportionate tachycardia. This theoretical calculation obviously has grave implications in terms of cardiovascular mortality.

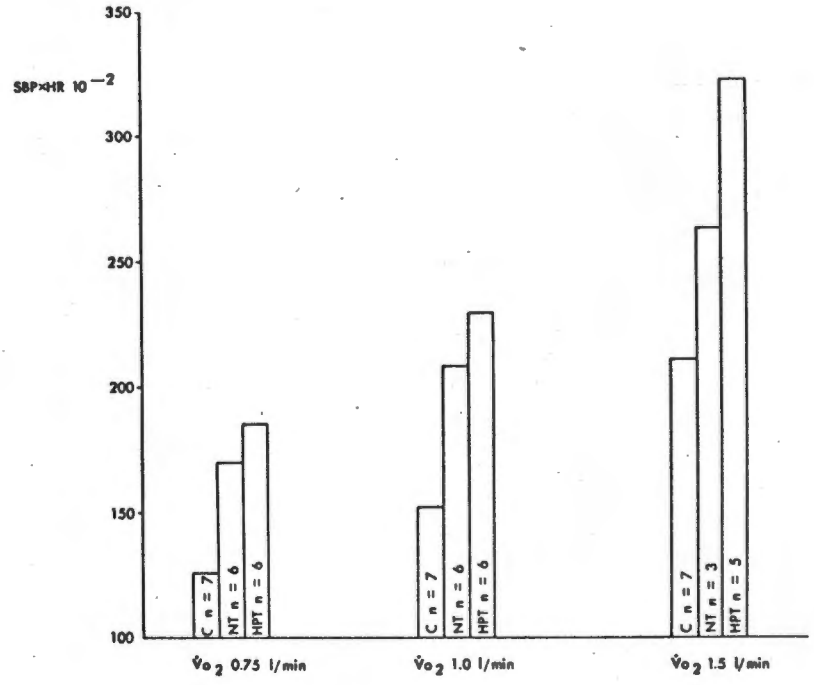

Figure 8 - Systolic Blood Pressure Heart Rate Product in Controls vs 'Normotensive' and Hypertensive Dialysis Patients

8.5 Conclusions

1. Healthy dialysis patients have reduced work performance associated with a more ready development of an RQ > 1 as exercise increases.
2. The patients develop disproportionate tachycardia on exercise compared to the controls, but in some the tachycardia is less apparent perhaps because of their blood pressure rise. Thus predictions of maximal oxygen consumption based on the heart rate are most unreliable.
3. Exercise testing is a simple method for unmasking those patients who will develop disproportionate

hypertension during everyday activity. The explanation for this hypertensive response may be partly age-related, but age is then influencing blood pressure responses far earlier than in the general population, and other factors must be involved.

4. The abnormally high heart rate systolic pressure product found in the dialysis group may well have relevance to the higher mortality from myocardial infarction that has been described in these patients.

CHAPTER 9

TECHNIQUES EMPLOYED FOR FURTHER HAEMODYNAMIC STUDIES

It soon became apparent that in order to understand why the dialysis patients developed abnormal circulatory responses to exercise, more detailed studies of their circulation were required. It was necessary that we at least should measure their cardiac output, body volumes and plasma renin activity.

9.1 Cardiac output technique

Guyton et al. (1973) have well reviewed the various methods of performing cardiac output estimations, their accuracy and reliability. In the early years of haemodialysis all patients had external arteriovenous shunts and hence dye of various sorts could easily and rapidly be injected through the venous limb of the shunt,while blood was withdrawn from the arterial end. This technique was validated by Coleman and Bower (1969). As experience with long-term dialysis increased, arteriovenous fistulae began to replace external shunts. With an established fistula it is now possible to thread a catheter into the pulmonary artery and perform cardiac output estimations by the direct Fick method or thermal dilution techniques. However, for various reasons both these methods were unsuitable for our patients. Although simple to perform, the indirect methods, such as rebreathing techniques and foreign gas methods, were rejected because of their poorer reproducibility and accuracy. Although the direct Fick is the prototype for cardiac output measurement, Wade and Bishop (1962) have found an excellent correlation between it and the dye-dilution methods ($r = 0,96$).

Charra et al., (1972, 1973), carefully validated a simple peripheral injection dye-dilution method using the arteriovenous fistula and compared the results to simultaneous right atrial injection of dye with withdrawal of blood from the brachial artery of the other arm. The correlation coefficient was 0,96, p value < 0,001, the regression coefficient 1,051 and the intercept -0,083 indicating that the peripheral injection gave cardiac output values very much the same as those obtained by the central injection. Because of its simplicity this seemed an ideal method for our patients.

Before measuring cardiac output by the method of Charra et al. it seemed wise to show that the blood from the arterial site of the fistula was in fact true arterial blood. In order to do this, blood was taken simultaneously and at the same rate from the proposed fistula site and a femoral artery puncture. Table I shows the pH, pCO_2 and PO_2 of the simultaneously taken fistula and femoral artery blood, measured on a Corning Eel pH Blood Gas Analyser 165. Patient B.B. has been entirely excluded from the mean results because there was an air bubble in the fistula blood syringe. As can be seen, there is no real difference between the mean pH and pCO_2 levels in the two blood samples, confirming that they were taken simultaneously. However, the pO_2 of the fistula blood is consistently about seven to eight mm Hg lower than the femoral artery blood, indicating some venous admixture. Two prospective patients were excluded from the cardiac output study because of a difference of greater than 10 mm Hg, but L.S. was retained because he was acting as an illustration of severe anaemia only, and is not in the haemodynamic series per se. This decision to exclude those cases where the pO_2 difference was more than 10 mm Hg was a purely arbitrary one, and the cut off chosen was not based on any scientific precedent because fistula validation has not previously been performed.

Table I - Comparison of Fistula and Femoral Artery Blood at Rest

Patient	Site	pH	pCO_2 (mm Hg)	pO_2 (mm Hg)
D.P.	Fistula	7,45	39,9	75,5
	Femoral	7,46	39,8	80,0
D.C.	Fistula	7,45	35,3	97,8
	Femoral	7,44	33,2	105,2
G.D.	Fistula	7,42	39,6	75,7
	Femoral	7,42	42,4	83,7
K.E.	Fistula	7,41	42,2	87,8
	Femoral	7,39	44,4	94,3
B.B.	Fistula	7,39	36,4	115,8 +
	Femoral	7,39	38,2	96,0
L.S.	Fistula	7,49	30,3	90,2
	Femoral	7,49	33,4	106,3
Mean	Fistula	7,44	37,5	85,4
	Femoral	7,44	38,6	93,9

+ All results excluded because of bubble in syringe.

During the initial clinical examination, while the subject is recumbent, a needle is inserted into the arterial side of the fistula as close to the anastomosis as is safe and a second needle as proximally as possible to act as the venous injection site. The fistula arterial blood is validated as above. Then, while sitting at rest, 20 ml arterial blood is drawn into a heparinized syringe for calibration purposes once the experiment is over. The patient is seated on the bicycle with the fistula arm supported by an arm rest. The venous needle is connected by a short stretch of tubing to three syringes linked by a three-way tap. One syringe is the reservoir for the dye; cardiogreen in a concentration of 5 mg/ml was used throughout the study. The second contains 50 ml heparinized saline for flushing and the third is an accurately calibrated injectate syringe which is set to deliver 1 ml of dye. The arterial needle is connected by a 100 cm plastic manometer line to a Gilford Densitometer and a constant speed withdrawal pump. The densitometer is linked to an X-Y Recorder, the recording speed of which is accurately measured before and after each experiment. Most workers using dye methods in dialysis patients have returned to the patient the blood withdrawn. This was not done in our case, because we could not guarantee the sterility of the curvette, and thus each patient lost approximately 100 ml of blood which was replaced as heparinized saline.

Four people were necessary for the smooth operation of the cardiac output estimations during exercise : one to control and record the exercise data, two for the rapid injection of the dye and the operation of the X-Y Recorder, and one controlling the withdrawal pump. Whether at rest or during exercise, the cardiac output measurements were made

during the fourth and final minute of the exercise load when a steady-state had been reached. The sequence of events during a cardiac output exercise test was as follows : a resting measurement sitting on the bicycle and then two measurements during exercise, one at a relatively low workload and the second either at peak exercise or at the penultimate workload. The blood pressure was measured at two and a half to three minutes and during the fourth minute the cardiac output was performed over the middle 20 seconds while the other exercise data was being recorded. Arterial blood for gases, oxygen content and haematocrit was taken at the end of the fourth minute. At the end of the experiment a three-point calibration is performed on blood previously withdrawn from the patient and free from dye and the injectate syringe carefully weighed to give the exact volume of dye delivered.

Figure 1 illustrates the actual curves obtained from a patient with an arteriovenous shunt (S.D. at rest), showing the obvious pulse inflections, compared to the completely smooth curve from a patient (K.E. at 25 Watts) with a fistula. All calculations were done by hand by routine methods. No curve was accepted unless there was a preceding stable horizontal baseline. Measurements were taken at 0,5 second intervals of the vertical height of the curve (dots on Figure 1) and plotted on semilog paper in order to determine the point of recirculation. This is shown in Figure 2 as two plotted curves from the same patient (K.E.) at rest and at 75 Watts. The figure also demonstrates the number of points available on the downstroke of the curve for extrapolation to baseline. This is particularly important at peak exercise when the cardiac output is high and the curves are small. No curve was accepted unless at least three points were available for extrapolation. The importance of validating the fistula arterial blood, the three-point

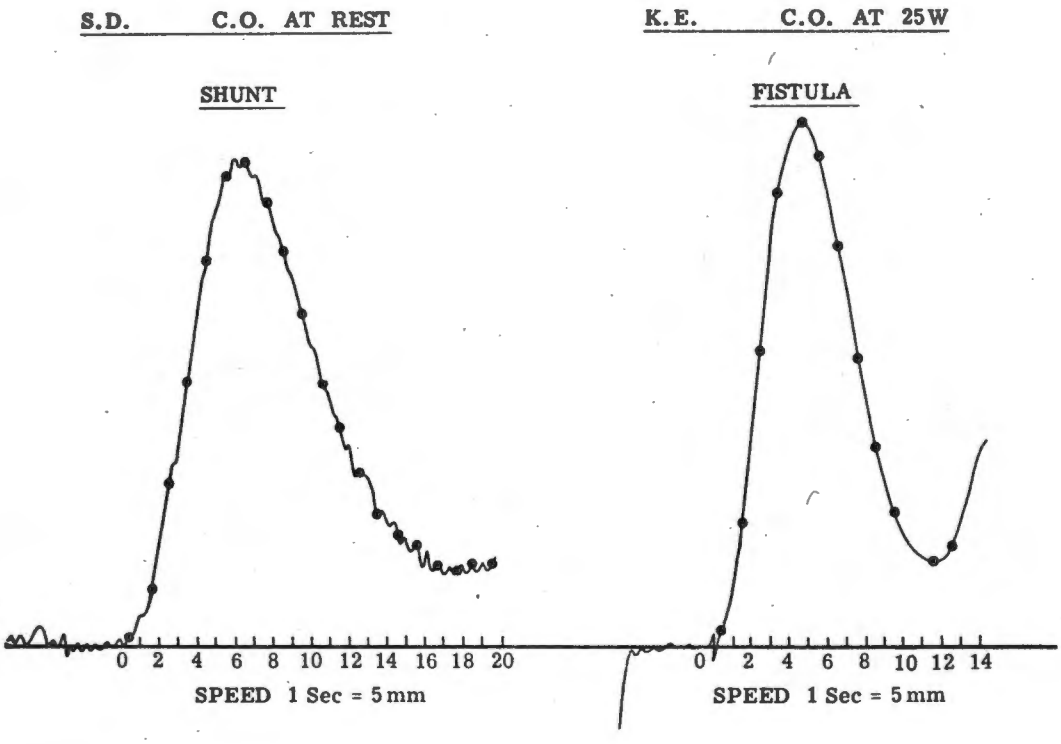

Figure 1 - Cardiac Output from Shunt and Fistula

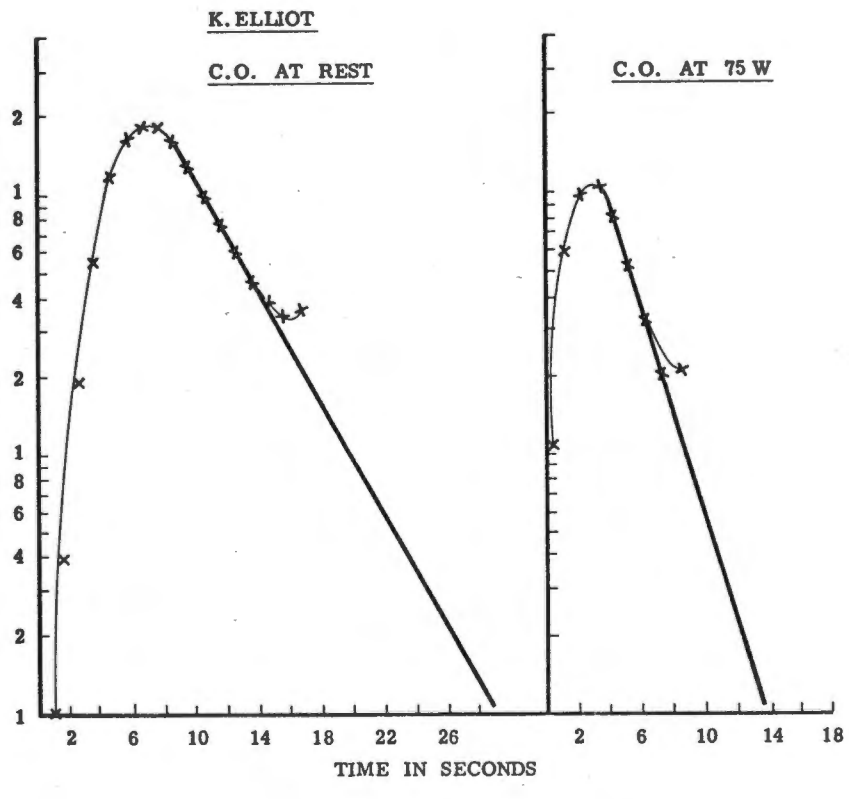

Figure 2 - Recirculation at Rest and on Exercise

calibration, the good quality curves obtained and at least three points on the downstroke of the semilog curve is stressed, because we were unable to perform our cardiac output estimations in duplicate due to the volume of blood that would be lost to these anaemic patients. The error of the method under these standardized conditions is probably less than 10 per cent.

After each cardiac output estimation, arterial blood is taken for oxygen content. This was measured in triplicate on a Lexington Oxygen Content Analyser together with haematocrit. From the Fick Equation

where C.O. (l/min) = $\frac{\dot{V}_{O_2} \text{ (ml/min)}}{A - V_O \text{ difference (ml/l)}}$

once cardiac output, oxygen consumption and arterial oxygen content are known, the venous oxygen content and the $A\text{-}V_O$ difference can be calculated. Stroke volume is obtained from the $\frac{C.O.}{H.R.}$ in ml/min. One patient with an arteriovenous shunt had measurements of direct systolic, diastolic and mean pressures made and hence total peripheral resistance could be calculated.

In any critical appraisal of haemodynamic data (Wade and Bishop , 1962; Guyton et al., 1973), it is important to appreciate that changes do occur in cardiac output with increasing age, and between the sexes. Increasing body surface area is associated with higher values, and hence it is important to standardize cardiac output, stroke volume and oxygen consumption as an index. Measurement of cardiac output, stroke volume and $A\text{-}V_O$ difference vary with posture and thus values obtained recumbent are not comparable to those obtained sitting. Normal control values were obtained from the literature (Åstrand et al. 1964; Ekblom et al. 1968) and

invasive haemodynamic studies were not performed on our own controls.

9.2 Measurement of body volumes

Since varying body volumes are vitally important in determining the haemodynamic responses, these were measured with or without cardiac output estimations in some patients. There is controversy about which body compartment correlates best with blood pressure in volume dependent hypertension, but probably at least two compartments should be measured. In terms of convenience to the patients who attended on an outpatient basis, we chose total body water and plasma volume, the latter then being combined with the peripheral venous haematocrit to give total blood volume.

For the estimation of total body water, a dose of 400 μCi tritiated water (H_3O) was drunk before exercise began. A baseline blood sample was taken from those who had had a prior estimation done. After the exercise test, blood was taken at three hours (the equilibration time) in the sitting position and the total body water estimated by standard methods. The measured total body water was compared to a predicted value obtained from Moore et al. (1963), based on sex, age and body weight.

Plasma volume was measured after exercise in the sitting position, by injecting 1 μCi I^{125} Human Serum Albumen and blood taken at 10 and 20 minutes to give a two-point calibration. Haematocrit was measured on a Microhaematocrit Centrifuge. Total blood volume was calculated,assuming that the whole body haematocrit is 90 per cent of that measured. Prediction values were taken from Nadler et al. (1962), based on height and age.

9.3 Estimation of plasma renin activity

The other vital determinant of blood pressure is the activity of the renin-angiotensin-aldosterone system and hence some measure of this system is necessary.

The easiest hormone to measure is plasma renin activity and this was done using a Squibb Immunotope Kit. In radioimmunoassay circles commercial kits have a slightly tainted reputation, but unless a particular assay is being used routinely, these kits provide a simple and economic alternative. Although the manufacturers quote a normal range and give figures for the reproducibility of the kit in other laboratories, it is important that each laboratory should establish its own normal range and validate the kit in their own hands. Accordingly, the coefficient of intra-assay variation of duplicates done on the first 200 consecutive samples and then four months later on a further 200 samples was five per cent. This figure compares very favourably with those quoted by other laboratories for standard non-kit methods. However, when this coefficient of variation was separated into that on samples with low activity and those with high activity the figures were five and 12 per cent respectively. Samples were not stored for any length of time, the longest being three weeks before assay, and thus interassay variation was not done. The lowest plasma renin level obtained in an anephric subject was 10 pg/ml/hr, while the highest reading obtained after dilution was 16,5 ng/ml/hr. The mean recovery of added amounts of standard of 10 to 640 pg to 21 samples of anephric serum was 95 per cent. Because of claims that a longer incubation period increases the yield, three hour incubation was compared to 20 hour, but no increased yield was found. Similarly, adjusting the pH of the kit from its own level of 7,4 to pH 5,5 made no difference to the final results.

In a small group of 11 healthy young subjects of both sexes, the mean result on a normal diet and after standing was 0,95 ng/ml/hr with a range of 0,5 to 1,64 ng/ml/hr. In nine salt depleted subjects, again tested erect, the mean was 2,2 ng/ml/hr (range 0,77 to 3,48 ng/ml/hr), while the same subjects tested after salt loading gave a mean of 0,41 ng/ml/hr (range 0,1 to 1,04). The dialysis patients were sampled at rest in the sitting position and again on peak exercise on the bicycle. The blood was immediately taken into cold EDTA tubes and separated on a cold centrifuge within five to 10 minutes of sampling and then deep frozen.

CHAPTER 10

BODY VOLUMES, HAEMODYNAMICS AND PLASMA RENIN ACTIVITY IN SELECT PATIENTS

10.1 Introduction

In Chapter 8 it was shown that a select group of fit haemodialysis patients had a reduced working capacity associated with disproportionate tachycardia and, in some, alarming hypertension compared to a matched control group. It was felt that the age difference (10 years) between the two subgroups and the difference in resting blood pressure could not completely account for the accelerating rise in systolic blood pressure in the hypertensive subgroup. It was thus important to assess the body volumes in relation to the plasma renin activity of the two subgroups, and to have some measure of their central haemodynamic status. Not all patients in each subgroup would agree to further study, while some agreed to volume and plasma renin activity estimations and not to the haemodynamic measurements. On all repeated tests the patients were again fully examined, had a chest X-ray, ECG and routine blood tests. Again none of the patients showed clinical circulatory overload. The results will be presented in such a way as to advance in a logical fashion the argument of this Thesis.

10.2 Body volumes, plasma renin activity and blood pressure

Table I shows that there are four patients in the 'normotensive' subgroup and five patients in the hypertensive subgroup and that two 'normotensives' had repeat body volume estimations, while one hypertensive was repeated. There is no significant difference between the mean

TABLE I - Body Volumes and Systolic Blood Pressure in the Two Subgroups

Patient	Date	lib	C.T.R.	Total Blood Volume			Total Body Water			Peak SPB	Peak H.R.
				Measured (litres)	Predicted (litres)	% Predicted	Measured (litres)	Predicted (litres)	% Predicted		
1. 'Normotensives'											
K.E.	12/74	9,8	37	3,67	4,59	80	37,6	38,7	97	210	166
K.E.	4/75	9,7	37	3,97	4,59	87	36,0	38,7	93	160	177
R.B.	4/75	5,7	48	4,25	4,49	95	-	-	-	170	169
R.B.	7/75	5,7	45	4,39	4,49	98	37,2	38,0	99	155	168
B.B.	16/75	7,8	36	4,38	4,43	99	37,6	35,8	105	155	172
G.F.	3/75	8,3	39	4,10	4,03	102	-	-	-	185	174
Mean		7,8	40	4,13	4,44	94	37,1	37,8	99	173	171
2. Hypertensives											
D.P.	12/74	8,1	49	5,01	4,45	113	38,6	37,1	104	230	177
D.P.	5/75	8,8	51	5,17	4,45	116	44,7	37,1	120	212	167
G.D.	3/75	6,9	50	7,27	5,34	136	48,4	39,7	122	190	152
P.R.	5/75	9,1	42	6,03	4,83	125	44,8	41,3	108	210	151
H.D.	12/74	9,5	43	4,37	4,32	101	39,9	38,9	103	220	140
D.C.	5/75	8,0	47	5,71	5,38	106	48,8	46,3	105	205	165
Mean		8,4	47	5,59	4,80	116	44,2	40,1	110	211	159

haemoglobin or cardiothoracic ratio of the two subgroups, but the mean levels of both are lower in the 'normotensives'. The measured values, the predictions and the measured value expressed as a percentage of the prediction is shown for total blood volume (T.B.V.) and total body water (T.B.W.). The 'normotensive' subgroup have significantly (Wilcoxon Test) lower volumes than the hypertensives, but it is noteworthy that the predicted values are also lower in the 'normotensive' subgroup, which is a reflection of their smaller body dimensions. The systolic blood pressure and heart rate shown is the value recorded at peak exercise, and again there is a significantly lower peak pressure achieved by the 'normotensives', but no significant difference in heart rate, although the mean is lower in the hypertensives. The differences for the predicted volumes, peak systolic pressure and heart rate together with the non-parametric statistics are illustrated in Figure 1. The 95 per cent confidence limits of the predictions are shown, those for total blood volume being $\pm$ 22 per cent and for total body water $\pm$ 16 per cent. Only two patients, G.D. and D.P., fall outside these limits suggesting that they may genuinely have clinical overload. Thus a superficial appraisal of these results leads to the conclusion that the hypertensive patients have a higher total body water and total blood volume than the 'normotensives', albeit at a subclinical level.

However, when the data is studied more critically, it is clear that the reproducibility both for the peak pressures and the heart rate in the repeat patients, K.E., R.B. and D.P. is very poor, whereas I was at pains to point out in Chapter 6 that the reproducibility is normally good. The explanation for this is that the final oxygen consumption varied between the two tests,being 1445 ml/min and 1802, 1297 and 1292, and

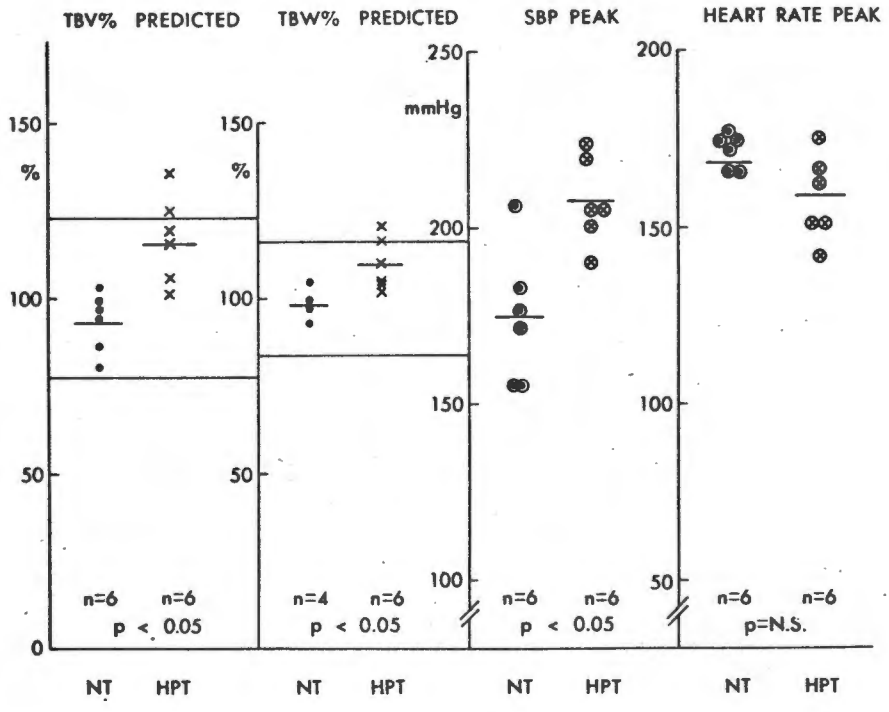

Figure 1 - Body Volumes and Systolic Blood Pressure in the Two Subgroups

1524 and 1423 respectively for K.E., R.B. and D.P. In order validly to compare different patients or the same patient, attention should be paid to the final oxygen consumption achieved and this should probably be expressed as an index. Similarly, to account for the differences in body volumes in the three patients, there were differences in body weight between the two occasions of up to 0,6 kg.

In order to overcome these objections, much of the same data is repeated in Table II together with the results of the plasma renin activity (P.R.A.) studied at rest and at peak exercise. Age is included to show that the discrepancy between the two subgroups is still 10 years.

Table II - Body Volumes, Plasma Renin Activity and Blood Pressure in the Two Subgroups

Patient	Age	BSA	Hb	C.T.R.	Peak $\dot{V}_{O_2}$ index (ml/min/m^2)	Total Blood Volume			Total Body Water			SBP		P.R.A. (ng/ml/hr)	
						Measured (litres)	Predicted (litres)	% Predicted	Measured (litres)	Predicted (litres)	% Predicted	Rest	Ex	Rest	Ex.
1. 'Normotensives'															
K.E.	30	1,77	9,7	37	1018	3,97	4,59	87	36,0	38,7	93	115	160	16,5	15,6
R.B.	21	1,73	5,7	45	747	4,39	4,49	98	37,2	38,0	99	108	155	4,13	4,13
B.B.	21	1,69	7,8	36	780	4,38	4,43	99	37,6	35,8	105	155	155	2,12	4,58
G.F.	20	1,60	8,3	39	770	4,10	4,03	102	-	-	-	150	185	4,52	5,03
Mean	23	1,70	7,9	39	829	4,21	4,39	97	36,9	37,5	99	132	164	6,8	7,3
2. Hypertensives															
D.P.	36	1,73	8,8	51	881	5,17	4,45	116	44,7	37,1	120	155	212	0,54	0,51
G.D.	35	2,02	6,9	50	742	7,27	5,34	136	48,4	39,7	122	125	190	0,29$^+$	0,45$^+$
P.R.	32	1,87	9,1	42	882	6,03	4,83	125	44,8	41,3	108	144	210	0,50	-
H.D.	34	1,71	9,5	43	616	4,37	4,32	101	39,9	38,9	103	150	220	0,48	0,56
D.C.	25	2,0	8,0	47	822	5,71	5,38	106	48,8	46,3	105	172	205	5,90	>5,29
Mean	32,4	1,87	8,5	47	789	5,71	4,86	117	45,3	40,7	112	149	207	1,5	1,7

The lower body weight and smaller C.T.R. of the 'normotensives' is in accord with the lower body volumes and lower predicted values. The higher mean oxygen consumption index in the 'normotensives' is partly due to the one high result (K.E.) and also partly due to the abnormally high body surface area of the hypertensives consequent on fluid retention. It may appear anomalous that in B.B. the resting systolic pressure and the peak pressure are identical and in K.E., in spite of his very high oxygen consumption index, the peak systolic pressure is in fact lower (160 mm Hg) than at a smaller oxygen consumption (210 mm Hg)shown in Table I when his $\dot{V}_{O_2}$ index was 812 ml/min/m^2. This apparent paradox was seen on a number of occasions when the systolic pressure actually began to fall as they neared peak exercise and some patients (all 'normotensives') complained of dizziness.

Of greatest interest is the behaviour of the P.R.A. in relation to the body volumes and blood pressure in the two subgroups. The actual values are shown in Table II and illustrated in Figures 2 and 3. In general those who have normal or low values of total body water and total blood volume, have high levels of P.R.A., but relatively normal blood pressures while the converse is true for those with high volumes. Thus P.R.A. seems to behave appropriately to the volume status and appears to be exerting no influence on the blood pressure. One exception is D.C. (Table II) who has a mildly elevated volume and yet a high level of plasma renin activity and his high blood pressure is probably maintained by both volume and renin factors. H.D. is a mystery, because in spite of the poorest exercise tolerance ($\dot{V}_{O_2}$ index 616 ml/min /m^2), he develops a very striking hypertension with normal volumes and a normal P.R.A. G.D., labelled with an asterisk, had his P.R.A. measured on a separate occasion when his

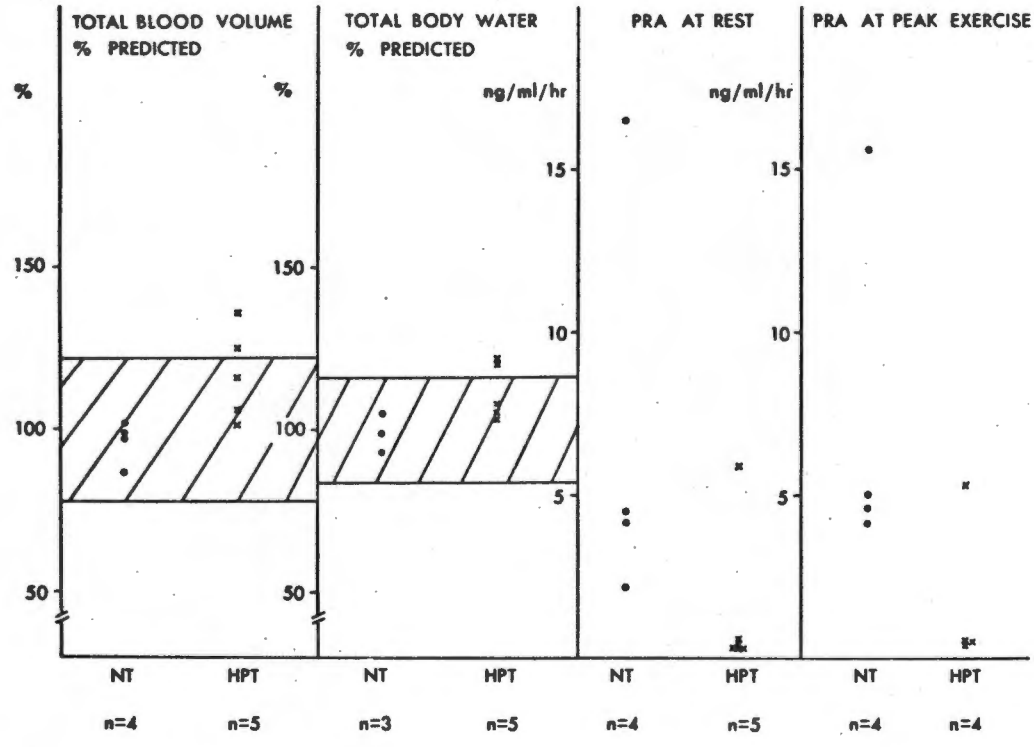

Figure 2 - Body Volumes and Plasma Renin Activity of 'Normotensive' and Hypertensive Subgroups

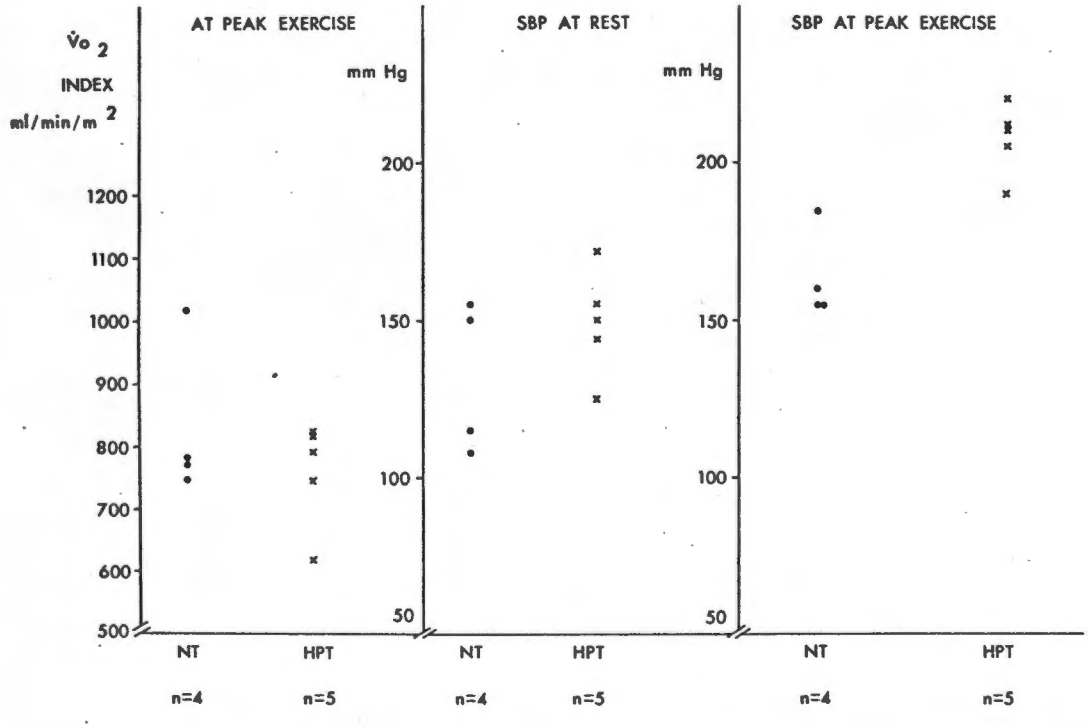

Figure 3 - Resting and Peak Exercise Systolic Blood Pressure and Oxygen Consumption Index

predicted total body water was 126 per cent which is comparable to that shown in Table II and has been included. It is noteworthy that there is no increase in the renin levels with exercise which corresponds with the general concept that a rise only occurs towards the end of exhausting exercise and elevated levels continue into the recovery period. For comparable P.R.A. values in normals subjected to salt loading and salt depletion see Chapter 9.

10.3 Conclusions

This section shows that we are dealing with a group of dialysis patients whose blood pressure is largely volume dependent and their renin-angiotensin system responds physiologically to volume changes. Thus, although the systolic pressures at rest are not strikingly different, on the equivalent exercise, the one group develops striking systolic hypertension due to volume expansion and not due to hyperreninaemia. It is of great practical importance that subclinical volume overload is uncovered by the blood pressure response to exercise testing.

10.4 Central haemodynamics, body volumes and blood pressure

On the same occasion as their volumes and P.R.A. were measured, six patients, two from the 'normotensive' subgroup and four hypertensives, agreed to have haemodynamic studies performed. Two of the hypertensive patients had repeat studies after they had changed their body volume and one additional patient, not from either subgroup, who was severely anaemic, was also assessed. One subject had an arteriovenous shunt and the remainder fistulae. The dye dilution technique for performing cardiac output was described in the last chapter, as was the method for

measuring arterial oxygen content. The various mathematical derivations have also been discussed.

Table III shows the haemodynamic studies in seven patients, two from the 'normotensive' subgroup, four from the hypertensive subgroup and one 'normotensive'anephric patient with severe anaemia. Other patient details such as age, body surface area, exact body volumes and P.R.A. at rest and on exercise may be obtained under the patients' initials from Table II of this chapter. It will be noticed comparing Tables II and III that the peak $\dot{V}_{O_2}$ index is different for K.E. and D.P.; this is because it was not always possible to perform cardiac output at the final workload. The additional patient, L.S., was a 25 year old man with a BSA of 1,88, a measured to predicted total blood volume of 111 per cent and total body water of 106 per cent and a P.R.A. of 0,03 ng/ml/hr. He was anephric with a resting pressure of 134/80 mm Hg and has been included for comparative purposes as a patient with severe anaemia (Hb 4,6 gm/100 ml)and virtually no circulating angiotensin. In Table III all the haemodynamic parameters are expressed as indices and the measured arterial oxygen content (Ao) and the calculated arteriovenous oxygen difference ($A\text{-}V_0\Delta$) in volumes per cent. P.R. had a shunt and his direct blood pressure measurements are shown together with the indirect.

In order to clarify the results they have been plotted as a scattergram in Figure 4, which shows the three indices and the $A\text{-}V_0\Delta$ for three subgroups, 'normotensives' (NT), hypertensives (HPT) and the one severely anaemic patient (AN). The resting values are shown without a circle while the results at the highest workload are circled. The blocks, labelled Ao, are the range in these patients for the arterial oxygen content at the highest workload during which haemodynamic measurements were made.

Table III - Haemodynamic Studies at Rest and on Exercise of Seven Patients

Patient	Hb	Volume	P.R.A.	Workload (Watts)	$\dot{V}_{O_2}$ Index (ml/min/m^2)	Cardiac Index (l/min/m^2)	Stroke Index (ml/min/m^2)	Ao (Vols. %)	A-$\dot{V}_{O_2}$ Δ (Vols. %)	H.R.	Sphyg.BP	Direct BP
1. 'Normotensive'												
K.E.	9,7	Low-normal	High	Rest	135	3,7	43	12,8	3,6	87	115/82	-
				25	336	6,5	63	12,4	5,2	104	126/86	-
				75	802	11,0	68	14,0	7,3	161	176/85	-
B.B.	7,8	Normal	High	Rest	154	5,0	47	9,6	3,1	105	155/105	-
				25	354	8,0	66	10,1	4,4	122	162/82	-
				90	780	11,7	68	9,8	6,7	172	155/45	-
2. Hypertensive												
G.D.	6,9	High	Low	Rest	90	2,5	31	8,0	3,6	81	120/75	-
				25	342	5,9	58	-	5,8	102	155/70	-
				75	742	7,9	52	-	9,4	152	190/70	-
D.P.	8,8	High	Low	Rest	189	4,1	47	10,6	4,6	87	155/98	-
				25	397	6,4	63	10,6	6,2	101	164/95	-
				75	818	8,4	56	10,8	9,7	150	200/92	-
P.R.	9,1	High	Low	Rest	189	3,9	44	12,7	4,8	89	144/100	170/115
				80	882	9,4	62	13,2	9,4	151	210/110	220/115
D.C.	8,4	High-normal	High	Rest	183	4,2	41	10,4	4,4	103	165/110	-
				25	395	6,1	53	11,4	6,5	116	175/100	-
				90	822	10,3	62	11,9	8,0	165	205/80	-
3. Anaemia												
L.S.	4,6	High-normal	Anephric	Rest	168	5,5	64	5,6	2,6	87	134/80	-
				20	334	8,7	86	6,1	3,8	102	145/65	-
				60	572	10,3	72	6,7	5,6	142	168/58	-

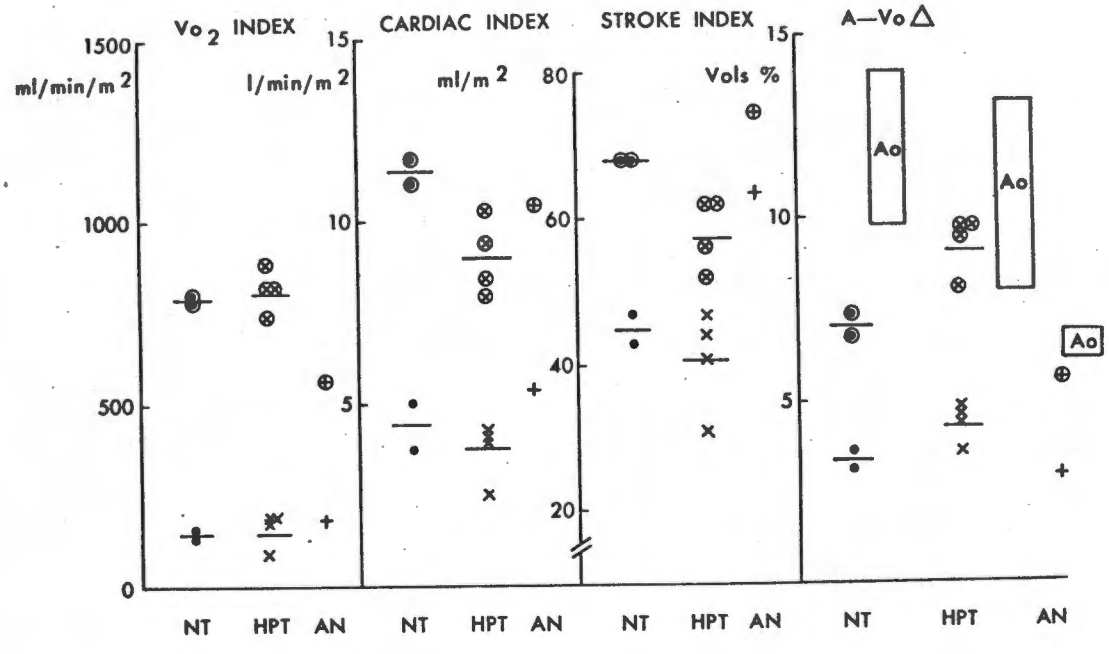

Figure 4 - Haemodynamics at Rest and on Peak Exercise of Seven Patients

Referring both to the actual data in Table III and its scattergram representation in Figure, it is clear that, although the results are similar at rest, marked differences are found during heavy exercise between the 'normotensive' and hypertensive subgroups ; their exercise $\dot{V}_{O_2}$ indices are comparable, but the 'normotensives' develop a much higher cardiac index and stroke index than the hypertensives, and at equivalent exercise the former have a lower A-$V_O\Delta$ than the latter. In the hypertensives the A-$V_O\Delta$ is approaching their arterial oxygen content, and thus their venous oxygen content is approaching zero. The single anaemic patient cannot perform the same workload as the other subgroups, but at this low load

has a disproportionately high cardiac index and stroke index and like the hypertensives is also running short of oxygen to supply his tissues. It should be remembered that the normal arterial oxygen content is about 20 Volumes per cent, the resting A-$V_{O}\Delta$ between five and 10 Volumes per cent and that at exhausting exercise 16 to 19 Volumes per cent. Obviously, the difference in our patients is due to their underlying anaemia. Thus in general terms the two 'normotensive' subjects develop a higher cardiac index and stroke index with less demand on their oxygen carrying capacity, while the hypertensives do the reverse. The severely anaemic patient not only has less work capacity, but is also extending his heart and his tissue oxygenation towards the maximum.

How does one attempt to disentangle the effects of the underlying anaemia and the varying degrees of circulatory volume overload ? In order to do this we must know both the normal haemodynamic response to exercise and the response of pure anaemics, unassociated with renal disease or volume overload. In the absence of our own controls for this, the data has been taken from the literature. I have combined the data of Åstrand et al. (1964) and Ekblom et al. (1968) to produce a group of 20 young males (mean age 23,7 years, range 20 to 30 years), who were physically fitter than my sedentary controls for the bloodless exercise tests, and who had cardiogreen cardiac output studies performed during sitting exercise on a bicycle. All results were corrected to $1m^2$. I have then used Wade and Bishop's (1962) collected series of 52 patients (no age given) with a mean haemoglobin of 6,5 gms/100 ml as pure anaemic controls. Their subjects were studied recumbent by various cardiac output methods, but I have taken a visual mean of their plotted results to give a rough indication of their haemodynamic response to exercise.

In addition L.S. shows the effect of severe anaemia in a dialysis patient, but note that his body volumes were elevated above the predicted level.

Figure 5 shows a plot of cardiac index against oxygen consumption index, but the scale of the latter is restricted to the range achieved by the dialysis patients and is thus much smaller than normal. The normal control results taken from the literature are shown as a mean ± 2 S.E.E. with the regression equation and correlation coefficient. The results of the pure anaemics (Wade and Bishop) and the single severely anaemic patient are shown by an open and a closed triangle respectively with the relevant haemoglobin level. The anaemics obviously have a high resting cardiac index and develop a hyperkinetic circulation on exercise. The other six patients fall between the anaemic hyperkinetic response and the normal response. The first important fact is that only one of the six has a high resting cardiac index, while all on exercise show a variable hyperkinetic response. The second striking fact is that this variable hyperkinetic response does not appear to correlate with the degree of anaemia; the patient with the lowest haemoglobin (G.D. 6,9) has the most 'normal' looking response while B.B. (Hb. 7,8) behaves like the pure anaemics.

This apparent paradox is clarified by Figure 6, which again shows the controls as a mean and the 95 per cent confidence limits and the anaemic patient L.S. (closed triangles). The response of the other six patients clearly depends on their degree of circulatory volume overload and the blood pressure pattern on exercise. The two 'normotensive', normovolaemic patients behave like pure anaemics, whereas the four hypertensive, hypervolaemic patients respond in a progressively more 'normal' fashion as their underlying volume increases, so that D.P.

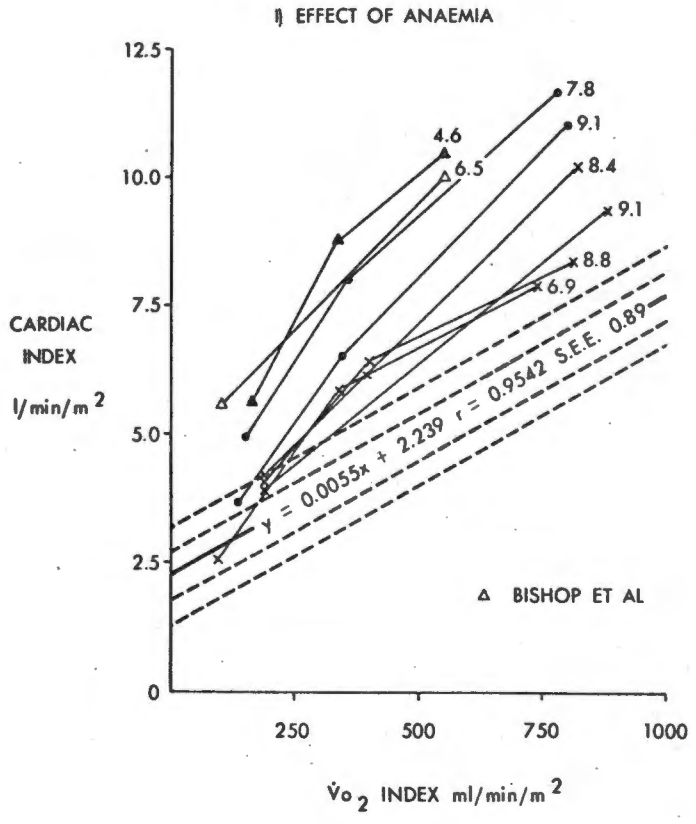

Figure 5 - Cardiac Index on Exercise in Controls[+] and Patients

+ Ekblom 1968, + Åstrand 1964

(Hb 8,8) and G.D. (Hb 6,9) who have the greatest subclinical overload have the least hyperkinetic circulation. Another point is that instead of the expected linear relationship between C.I. and $\dot{V}_{O_2}$ index on exercise, G.D. and D.P. show a broken response as if the excess volume becomes more and more restrictive as exercise progresses. The immediate inference is that subclinical volume overload and the development of accelerating hypertension during exercise in some way prevents the development of a hyperkinetic response appropriate to the underlying anaemia. It is well known (Wilcken et al., 1964) that increased impedance and afterload

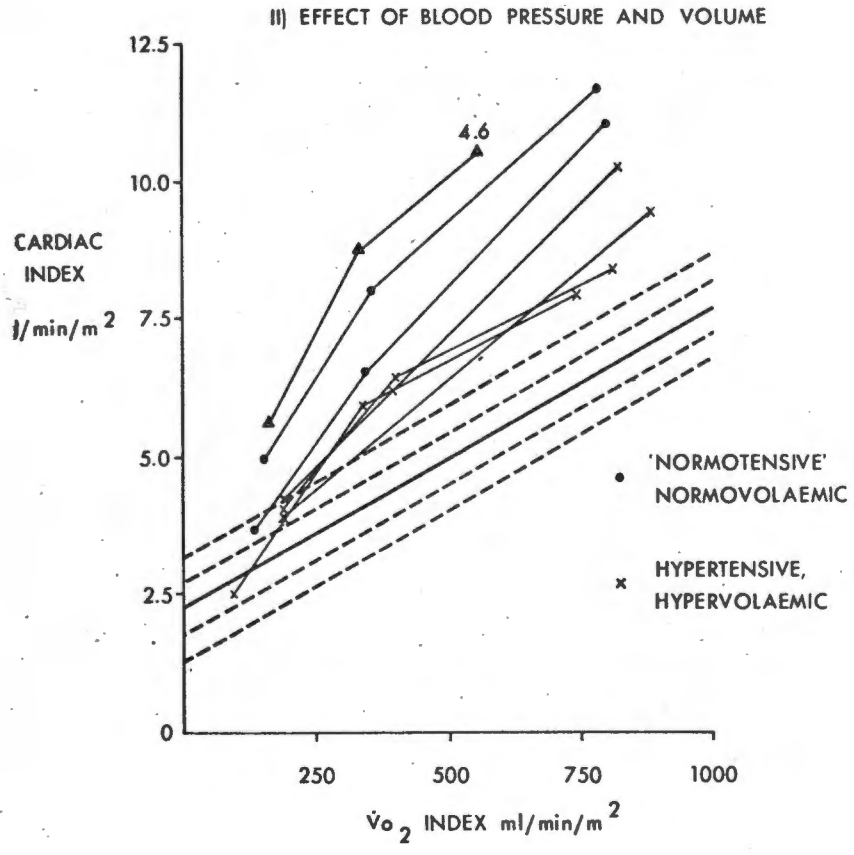

Figure 6 - Cardiac Index on Exercise in Controls+ and Patients

+ Ekblom 1968 +Åstrand 1964

will depress the cardiac output and it has been shown (Roy et al., 1963; Duke and Abelmann, 1969) in the pure anaemic situation that methoxamine induced vasoconstriction causes a fall in the high cardiac output and a concomitant rise in pressure. The temptation to attribute the depressed cardiac index of our hypervolaemic, hypertensive patients to some sort of peripheral 'waterlogging' (Tobian et al., 1969) with increased impedance is difficult to resist. On the other hand the two 'normotensive', normovolaemic patients are behaving like pure anaemics, with a hyperkinetic

circulation which may only be evoked by exercise.

If there is peripheral 'waterlogging', then once the excess volume is removed by dialysis, not only should the blood pressure fall but so should the peripheral resistance, and the cardiac output should become appropriate to the new haemoglobin value. Two patients, G.D. and P.R., the former with a fistula and the latter with a shunt, were willing to be restudied. They were both initially hypertensive and overloaded and were requested gradually to reduce their body weight on dialysis. The background data to these repeat studies is shown in Table IV. As is seen G.D. actually gained weight over the three month interval, but the volume increase occurred in total body water with a return to normal of his blood volume. Thus there was a redistribution of his volumes, but he still falls outside the 95 per cent confidence limits of prediction for total body water. P.R. on the other hand lost 4 kg weight and reduced both his body volumes to the predicted normal. The haemoglobin of G.D. remained the same at 7 gm/ml but in P.R. it rose from 9,1 to 12,5 following ultrafiltration and his P.R.A. also responded with an appropriate rise to the volume depletion.

Table V and Figure 7 show the haemodynamic results at rest and different workloads for the two patients. As illustrated on previous graphs the results of the cardiac index are plotted against oxygen consumption index with the normal haemodynamic data and the one severely anaemic patient as reference points. In Figure 7 G.D. (labelled B_1 and B_2), whose overall weight increased but whose haemoglobin remained the same, showed the same paradoxically low cardiac index response at equivalent oxygen consumption on both occasions, confirming the reproducibility of the observation. P.R. (labelled A_1 and A_2) who reduced

Table IV - Repeat Haemodynamic Studies in Two Patients - Volume and Plasma Renin Activity

Patient	Date	Wt. (kg)	Hb	C.T.R.	Total Blood Volume			Total Body Water			P.R.A. (ng/ml/hr)	
					Measured (litres)	Predicted (litres)	% Predicted	Measured (litres)	Predicted (litres)	% Predicted	Rest	Peak Ex.
G.D.	3/75	87,5	6,9	50	7,27	5,34	136	48,4	39,7	122	-	-
	6/75	91,2	7,0	50	5,11	5,34	96	50,2	39,7	126	0,29	0,45
P.R.	5/75	72,5	9,1	42	4,83	4,83	125	44,8	41,3	108	0,50	-
	7/75	68,4	12,5	37	4,70	4,70	98	40,4	39,6	102	0,99	2,0

Table V - Repeat Haemodynamic Studies in Two Patients - Cardiac Output and Blood Pressure

Patient	Date	Workload (Watts)	$\dot{V}_{O_2}$ I (ml/min/m^2)	C.I. (l/min/m^2)	S.I. (ml/min/m^2)	A_O (Vols. %)	A-$V_O\Delta$ (Vols.%)	H.R.	Sphyg BP	Direct BP
G.D.	3/75	Rest	90	2,5	31	8,0	3,6	81	120/75	-
		25	342	5,9	58	-	5,8	102	155/70	-
		75	742	7,9	52	-	9,4	152	190/70	-
	6/75	Rest	129	2,4	31	8,6	5,3	79	138/92	-
		25	331	5,0	51	8,8	6,7	97	158/85	-
		75	742	7,2	56	9,1	9,5	129	195/85	-
P.R.	5/75	Rest	189	3,9	44	12,7	4,8	89	144/100	170/115
		80	882	9,4	62	13,2	9,4	151	210/110	220/115
	7/75	Rest	176	2,0	19	14,8	8,9	105	114/85	121/80
		20	405	3,7	32	15,8	10,8	115	130/85	130/92
		60	639	5,0	35	16,0	12,7	145	150/85	168/92

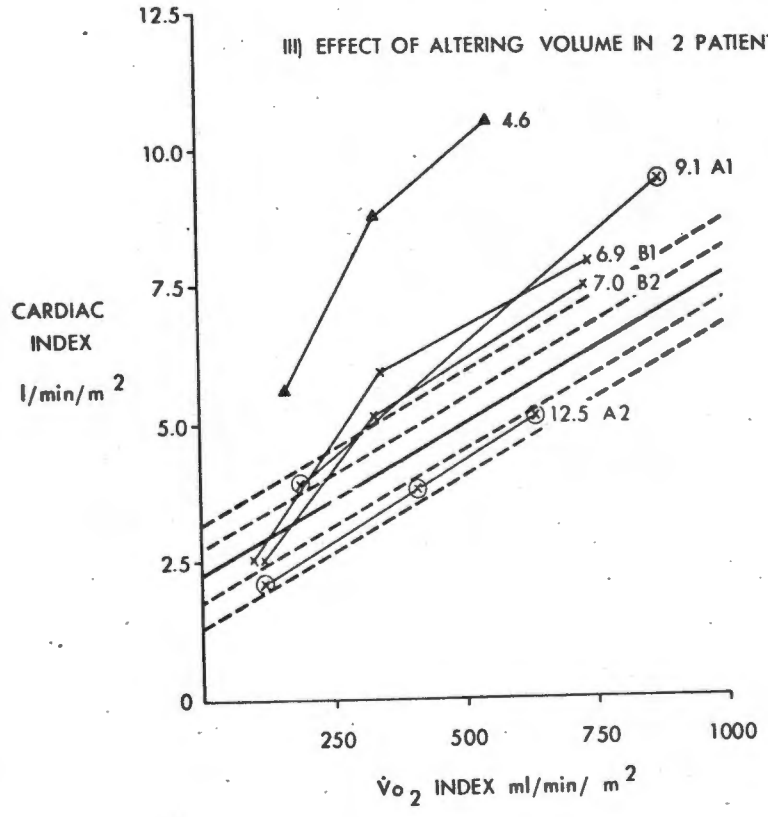

Figure 7 - Cardiac Index on Exercise in Controls+ and Patients

+ Ekblom 1968 + Åstrand 1964

his volume to the predicted level, increased his haemoglobin from 9,1 to 12,5 gm/100 ml. Over a six month period a year previously his haemoglobin ranged between 11 and 12 gm/100 ml, so the new value is not merely haemoconcentration and this is borne out by the real increase in arterial oxygen content (Table V). In the normovolaemic state, his blood pressure response is lower than before, but not quite in the normal range. However, his cardiac output response falls from hyperkinetic levels on exercise to within the lower range of normal. The workloads at which cardiac index were measured are different on the second occasion, so

that the figures cannot directly be compared, but it is clear that, although the response is now normal, his work performance is worse.

Attention must now be paid to the behaviour of the calculated stroke index of the two subgroups as a whole and in particular of the two patients who had repeat central haemodynamics performed. Figure 8 shows the stroke index plotted against the oxygen consumption index including a visual mean and the range of the normal results taken from Åstrand et al. (1964) and Ekblom et al. (1968). In sitting as opposed to recumbent exercise, the stroke volume rises early and then reaches a plateau. As can be seen the two 'normotensive' patients lie towards the upper end of the range, while the four hypertensives are well within the normal range on exercise, but the most overloaded patients (G.D. represented as B_1 and D.P.) actually show a fall on peak exercise, confirming the increasing afterload. When G.D. is repeated (B_2) there is a more normal stroke index response possibly related to his now normal total blood volume. However, when P.R. is repeated (A_2) his stoke index falls well below the normal range, suggesting that he has reduced his body volume too drastically, and, although he is just able to maintain a normal cardiac output it is at the expense of tachycardia and an abnormally low stroke volume. Circumstantial evidence for relative dehydration was the fact that his shunt clotted at the lower body volumes. If he was relatively dehydrated this would account for his poorer effort tolerance and the abnormally low stroke volume in the face of an improved haemoglobin. Also his $A\text{-}V_0\Delta$ is greater than before.

On the second occasion P.R. had an entirely normal resting blood pressure but the response on exercise, although much improved, was still above control levels, even when his indirect measurements only are

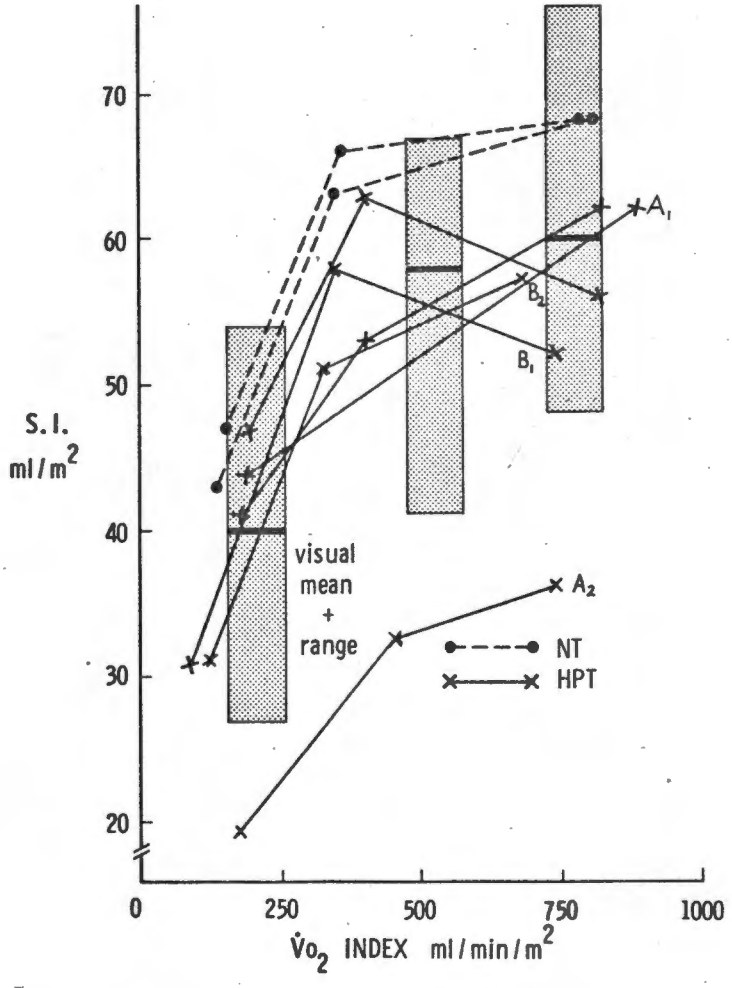

Figure 8 - Stroke Index in Controls[+] and eight Patients

+ Ekblom 1968 + Åstrand 1964

considered. Figure 9 shows his calculated total peripheral resistance in arbitrary units ($T.P.R. = \frac{M.A.P. \times 80}{C.O.}$) plotted against the normal range again taken from Åstrand and Ekblom. The results are very surprising. On the first occasion, when he was hypertensive, hypervolaemic and moderately anaemic (Hb 9,1 gm/100 ml) his total peripheral resistance is just above the normal range. On the second occasion, when he is normovolaemic, less hypertensive and less anaemic (Hb 12,5) the T.P.R. is even higher. Thus the hypothesis of simple 'waterlogging' of the peripheral vasculature in

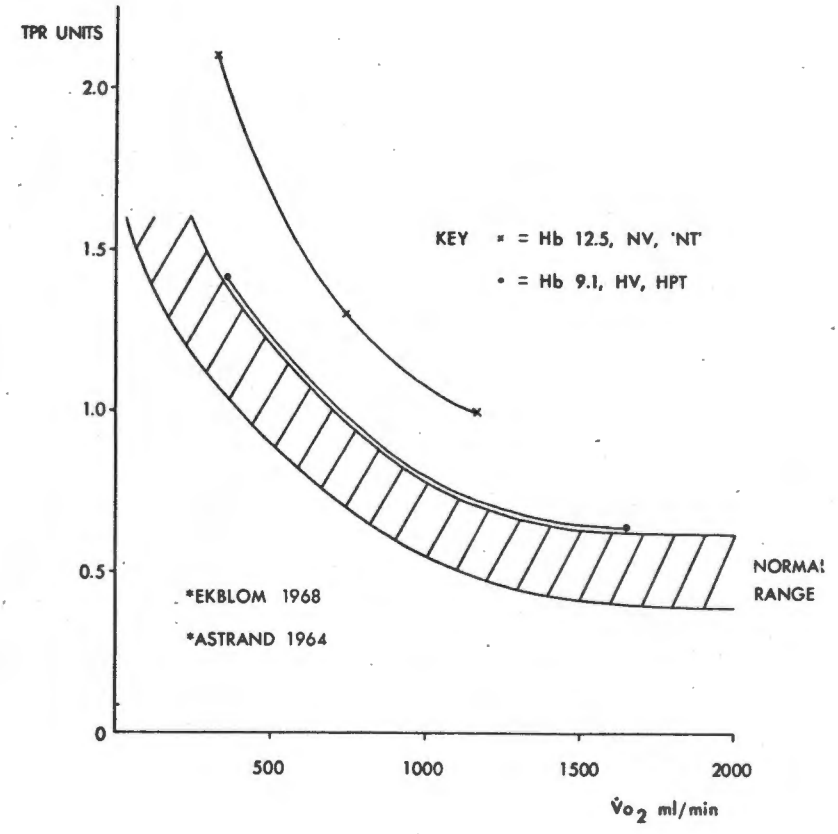

Figure 9 - Calculated Peripheral Resistance in Controls + and one Patient - Influence of Volume and Haemoglobin

+ Ekblom 1968 and °Astrand 1964

volume overload is no longer tenable, since any excess water should be ultrafilterable and removed by dialysis as the other body volumes are reduced. Therefore other factors or some other peripheral vascular change must be present.

It is well appreciated that increasing blood viscosity will also increase resistance. There was an increase in true haemoglobin with volume depletion from 9,1 to 12,5 gms/100 ml or a measured haematocrit increase from 28 to 38 per cent, but this change reflects only a small increase in

viscosity. Also with the volume depletion his resting P.R.A. increased from 0,5 to 0,99 ng/ml/hr. and there would be a corresponding increase in circulating angiotensin II levels, which could account for some of the increased peripheral resistance. Finally, because of the age difference between the two subgroups, it is possible that some more permanent structural alteration may be present and a hypothesis to account for this will be presented later.

10.5 Conclusions

1. It has been established that the 'normotensive' subgroup who are 10 years younger and have a slightly lower haemoglobin level, have body volumes much closer to their predicted level than their hypertensive counterparts, who, although not clinically overloaded, have expanded volumes. The plasma renin activity responds appropriately to the volume status and the hypervolaemic, hypertensive patients have low levels indicating that the hypertension is largely volume dependent.
2. With the exception of one patient, the cardiac index and stroke index fall within the normal range at rest.
3. On exercise all patients develop a variable hyperkinetic circulation. Those who are normotensive and normovolaemic become markedly hyperkinetic and behave like pure anaemics whose underlying total blood volume is normal. The hypervolaemic hypertensives develop a paradoxically more 'normal' response suggesting that the increased afterload depresses the anticipated hyperkinetic response.

4. All patients have a lower than normal arterial oxygen content due to their anaemia. However, the hypertensives deplete their venous oxygen content more than the 'normotensives' on equivalent exercise. Thus the 'normotensives' rapidly reach their maximal cardiac output while the hypertensives run out of oxygen with which to supply their tissues.
5. Two repeat cardiac output studies were performed. The one patient did not fundamentally change his overall body volume or haemoglobin and his cardiac index response was the same. The other patient not only became normovolaemic but in the process increased his haemoglobin by 3,4 gm/100 ml. His cardiac output response became normal and his blood pressure dropped to normal levels at rest, but not completely to normal on exercise. Surprisingly, there was a rise in calculated total peripheral resistance on the second occasion, indicating that simple ultrafilterable 'waterlogging' alone is not the explanation for the high resistance.

CHAPTER 11

THE VENTILATORY RESPONSES AND THEIR BEARING ON THE ABNORMALITIES FOUND ON EXERCISE

11.1 Introduction .

During exercise in normal subjects ventilation ($\dot{V}_E$) increases linearly with $\dot{V}_{O_2}$ or carbon dioxide production ($\dot{V}_{CO_2}$), until very heavy work is performed when the $\dot{V}_E$ increases disproportionately. The exact mechanisms controlling the rise in $\dot{V}_E$ are uncertain, but there must be an interplay of chemical (pH, pCO_2 and pO_2) and neuromuscular factors. However, it is known that only during very heavy exercise do the pH, pCO_2 and pO_2 drop (Wasserman et al., 1967) and this is accompanied by excess lactic acid production.

A number of disorders of pulmonary function have been described in patients on haemodialysis. The most important of these are due to circulatory volume overload which may progress to frank pulmonary oedema. Gibson (1966) studied seven patients, five with chronic renal failure who had both the clinical features and the radiological changes of pulmonary oedema, with right heart catheterisation. He found that the pulmonary vascular pressures were lower than those observed in acute pulmonary oedema due to rheumatic valvular disease and assumed the presence of increased pulmonary capillary permeability in renal failure. Guz et al. (1966) studied a patient with acute glomerulonephritis who was in clinical heart failure and had radiological evidence of pulmonary oedema. He was mildly anaemic (haematocrit 36 per cent), but had a normal cardiac output

and a normal arteriovenous oxygen difference during exercise over a wide range of oxygen consumption. They concluded that, in spite of a high venous pressure, the pumping capacity of the heart was normal. Crosbie and Parsons (1973) have also pointed out that the lungs of dialysis patients can accommodate a considerable amount of fluid before changes suggestive of pulmonary oedema are seen in the cardiac output, the alveolar-arterial oxygen gradient ($A\text{-}a_o$) and the dead space/tidal volume ratio (V_D/V_T). On the other hand Stănescu et al. (1974) have shown that in patients studied predialysis the peak expiratory flow rate was lower while the closing volume was significantly higher than the normal even when the vital capacity, the total lung capacity and the airway resistance were normal, and the patients had no cough and a normal chest X-ray. Zidulka et al. (1973) found in more overloaded patients that their lung volumes were reduced with a normal mid-expiratory flow rate and increased closing volumes, suggesting accumulation of oedema around the small airways. Thus in the absence of direct pulmonary artery and ventricular pressure measurements it is very difficult to assess when fluid overload causes actual heart failure. Three of the best indirect measures of interstitial/alveolar oedema are changes in the pCO_2 which indicate excessive hyperventilation and/or changes in the $A\text{-}a_o$ gradient and V_D/V_T ratio indicating respectively impairment of oxygen diffusion and wasted ventilation. We therefore studied these indirect parameters to determine if the flattened cardiac output response seen in the hypertensive hypervolaemic group was due to actual heart failure.

Other ventilatory abnormalities seen in haemodialysis patients include cyclical changes in pH and total bicarbonate in relation to each dialysis : they may become acidotic predialysis with pulmonary hyperventilation and alkalotic postdialysis with hypoventilation. Most dialysate solutions

now contain acetate (35-40 mEq/l) which is rapidly metabolised during dialysis producing a degree of metabolic alkalosis, hypoventilation and hypoxaemia (van Ypersele de Strihou et al., 1973). Others claim that the postdialysis hypoxaemia is not only due to pH changes and have evidence to suggest that there is pulmonary ventilation-perfusion imbalance as well (Torrance, et al., 1974; Hurwitz et al., 1974). Other more specific problems such as pulmonary metastatic calcification, pleural effusions and increased pulmonary infection also occur in dialysis patients.

In pure anaemia Housley (1966) studied seven patients with a mean haemoglobin of 4,7 gm/100 ml and found no hypoxia and normal alveolar ventilation at rest. Cotes et al. (1972 a) measured transfer factor and ventilation in 20 women during exercise with iron deficiency anaemia (Hb 8-9 gm/100 ml) before and after iron therapy. Their exercise ventilation was normal, but the transfer factor improved after therapy. However, other workers (Anderson and Barkve, 1970; Ekblom et al., 1972) agree that during exercise there is increased acidosis due to lactic acid and hence greater hyperventilation. In considering the response of dialysis patients to exercise the combined problems of volume overload, acid-base changes and anaemia must be borne in mind.

11.2 Ventilatory results at rest and on exercise

Table I gives the data of the 12 select males, now divided into the 'normotensive' and hypertensive subgroups, with respect to age, BSA, haemoglobin, C.T.R., FEV_1, FVC, FEV_1/FVC ratio and where available the peak flow rate and the flow volume curve. The FEV_1, FVC, peak flow rate and flow volume curve were performed before exercise on a Vertek VR 5000 Lung Function Computer and if they are compared to the control data shown in Chapter 8, Table V, it will be seen that there is no significant

Table I - Data on Twelve Select Male Patients

Patient	Age (years)	BSA	Hb (gms/100ml)	C.T.R. (%)	$F.E.V._1$ (l)	F.V.C. (l)	$F.E.V._1/F.V.C.$ Ratio	Peak Flow Rate (l/sec)	Flow Volume Curve
1. 'Nomotensives'									
R.B.	20	1,73	5,7	48	4,11	4,68	88	-	-
K.E.	30	1,77	9,7	37	4,58	5,62	82	-	-
A.P.	35	2,06	10,3	50	2,72	3,67	74	4,96	N
B.B.	21	1,69	7,8	36	4,5	5,07	89	8,76	N
M.B.	25	2,00	8,5	41	4,4	6,42	69	6,45	N
G.F.	20	1,60	8,3	39	4,29	5,12	84	9,62	-
2. Hypertensives									
G.D.	35	2,02	6,9	50	3,75	4,64	81	9,33	N
P.R.	32	1,87	9,1	42	3,45	4,81	72	8,98	-
D.P.	36	1,74	8,8	51	3,87	4,79	81	-	-
H.D.	34	1,71	9,3	43	3,15	4,14	76	-	-
A.D.	39	1,83	9,5	51	3,64	4,25	86	9,82	N
D.C.	25	2,0	8,0	47	4,00	5,14	78	10,11	? Obstructive

N = Normal appearance

difference between the patient and control groups. Two controls and four of the patients were smoking at the time of the study. Although no predicted values are given for the peak flow rates, these fall within the normal limits. Thus at rest there is no gross evidence of either restrictive or obstructive lung disease.

Table II shows the ventilatory results of the bloodless exercise test with the $\dot{V}_E$ at $\dot{V}_{O_2}$ 0,75, 1,0 and 1,5. As can be seen, there is no marked difference between the patients and the controls, thus ventilation is not the major factor limiting their exercise tolerance. Although there is no statistical difference between patients and controls, the patients have a higher mean level of ventilation at each point and it is possible that they in fact do have mild hyperventilation. When the $\dot{V}_E$ is broken down into respiratory rate and tidal volume (not shown here) there was again no significant difference between the patients and controls either at rest or at $\dot{V}_{O_2}$ 1,0. From the simple exercise test there is no indication of any striking hyperventilation in the dialysis group.

Plasma lactate levels were measured in nine of the 12 patients at rest and during each workload by a Boehringer Mannheim Kit which uses an enzymatic method. These arterial levels were then compared with the mean and range of Åstrand (1964) and Ekblom's (1968) levels obtained during cycling in healthy young males. The lactate method used by these authors was also an enzymatic one, but the technique did differ in some respects. As is seen from Figure 1 the patient levels are generally lower at rest and during mild exercise than the controls, but on heavier exercise the patients develop a more pronounced lactic acidosis. It is also noteworthy that the rate of rise of plasma lactate appears to be the same in the 'normotensive' (dots) and hypertensive (crosses) subgroups. Although these results were not submitted to statistical analysis, the increased

Table II - Ventilation Results in Patients and Controls

Patients	$\dot{V}_E$ 0,75	$\dot{V}_E$ 1,0	$\dot{V}_E$ 1,5	Controls	$\dot{V}_E$ 0,75	$\dot{V}_E$ 1,0	$\dot{V}_E$ 1,5
R.B.	22	31	-	N_5R	20	28	41
K.E.	26	36	56	N_6R	32	36	45
A.P.	17	24	40	N_7	20	25	37
B.B.	27	37	-	N_8	17	22	34
M.B.	21	29	44	N_{10}	21	28	41
G.F.	23	32	-	N_{13}	18	22	31
G.D.	22	30	46	N_{15}	24	34	53
P.R.	21	30	47	N_{16}	23	33	53
D.P.	19	26	39	N_{18}	20	26	37
H.D.	28	38	-	N_{19}	18	23	33
A.D.	19	26	41	N_{20}	22	29	43
D.C.	19	25	36	N_{24}	17	23	35
Mean	22	30,3	43,6		21	27,4	40,3
I S.D.	3,5	4,7	6,2		4,1	4,8	7,3
P value	+N.S.	++ 0,2-0,1	+++ N.S.		+ N.S.	++0,2-0,1	+++ N.S.

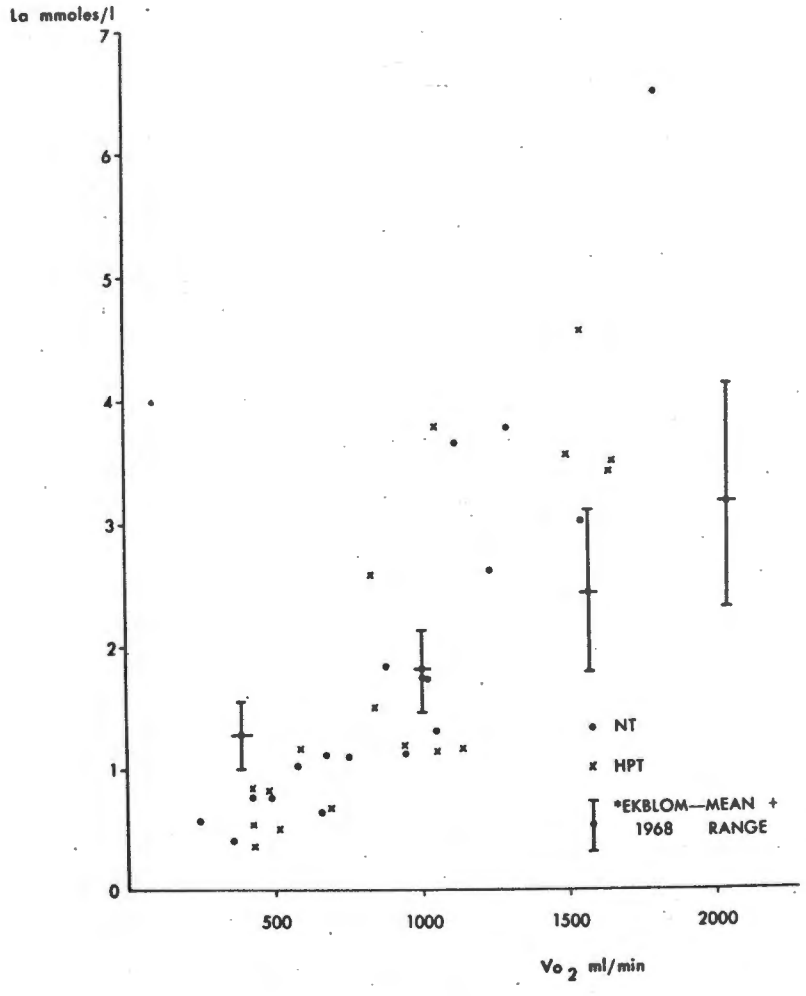

Figure 1 - Arterial Lactate Levels during Exercise in Controls+and Patients

+ Ekblom 1968 and + Åstrand 1964

lactic acid levels confirm the finding of a higher respiratory quotient in the patient group (Chapter 8) and hence the development of premature anaerobic metabolism. Pure anaemia is associated with increased exercise lactic acidosis and it will be remembered that Lange et al. (1973) demonstrated that the increased lactate and pyruvate levels found on exercise in dialysis patients could be brought within the normal range by correcting the anaemia. Lastly, lactic acidosis is known to be associated with muscle fatigue, which was the predominant complaint of the patients after exercise.

Table III shows more detailed respiratory studies in the six patients on whom the haemodynamic investigations were performed. The single anaemic

patient and the repeat studies on G.D. and P.R. are not shown. For details of age, BSA, Haemoglobin and C.T.R. please refer to Table I. The results of each parameter are given at rest (0 Watts or rolling basal) and peak exercise, and the final $\dot{V}_{O_2}$ index is given for comparison. Respiratory rate (R.R.) was measured and tidal volume (V_T) calculated from the $\dot{V}_E$. The pH and blood gas tensions were measured on arterial blood from the fistula in five patients and the shunt in patient P.R. It should be remembered that the arterial fistula blood was compared to femoral artery blood at complete rest lying down and a 8 mm Hg pO_2 difference was consistently found (Table I, Chapter 9), indicating that there was a small venous admixture. The rolling basal pO_2 results are therefore a lesser underestimate, but the peak exercise results with the hyperkinetic circulation are probably true since it was previously shown (Chapter 7, Section 2) that during exercise the flow through the fistula becomes smaller relative to the overall increase in the cardiac output and hence any venous admixture would become proportionately less. The physiological dead space (P.D.S.), the dead space/tidal volume ratio (V_D/V_T) and the alveolar-arterial oxygen gradient ($A\text{-}a_o$) were calculated by computer using standard formulae. The important results are also presented graphically in Figures 2 and 3, the second showing the exercise response of the pO_2 and pCO_2 and the third figure the response of the $A\text{-}a_o$ and the V_D/V_T. Jones et al. (1966) give normal values for the response of P.D.S., V_D/V_T and $A\text{-}a_o$ during exercise. The P.D.S. increases during exercise, but once the $\dot{V}_{CO_2}$ is more than 1 l/min V_D/V_T falls due to a disproportionately increased V_T. The $A\text{-}a_o$ does not change from the resting level of between five and 20 mm Hg until the $\dot{V}_{O_2}$ is more than 1,5 l/min when it begins to rise. The V_D/V_T and $A\text{-}a_o$ are indications of the matching of ventilation to perfusion and hence indirect indices of pulmonary venous pressure. Jones' normal range is indicated in Figure 3. The patient labelled with an asterisk in the two figures is G.D. who had the greatest measured volume overload and the least hyperkinetic response to exercise.

Table III - Respiratory Studies in Two 'Normotensive' and Four Hypertensive Patients

Patient	$\dot{V}_E$(l/min)		R-R (min)		V_T (ml)		pO_2 (mm Hg)		pCO_2 (mm Hg)		pH	
	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex
1. 'Normotensives'												
K.E.	10,4	47,6	12	27	868	2832	77,8	106	40,3	27,2	7,42	7,39
B.B.	11,6	57,8	12	44	963	1311	91,8	97,4	38	29,3	7,38	7,33
2. Hypertensives												
G.D.	10,4	46,4	14	32	742	1449	85,7	97,8	39,6	37,6	7,42	7,40
D.P.	11,4	34,8	16	28	582	1587	87	91	39,5	36,2	7,45	7,42
P.R.	12,7	52,4	9	25	1415	2095	98,4	104,6	31,1	29,4	7,37	7,31
D.C.	14,4	41,5	18	25	802	1661	90,5	94,7	40,3	37,3	7,37	7,35

Patient	Lactate (mmole/l)		P.D.S.(ml)		V_D/V_T (%)		A -a_o (mm/Hg)		Final $\dot{V}_{O_2}$ Index
	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	(ml/min /m^2)
1.'Normotensives'									
K.E.	0,56	6,49	325	527	37,4	11,5	24	19	1018
B.B.	0,78	3,65	272	255	28,2	19,5	10,9	24,7	780
2. Hypertensives									
G.D.	0,37	3,55	160	350	17,1	24,1	25,2	9,3	742
D.P.	0,54	4,60	224	193	17,3	12,1	10,8	21,4	881
P.R.	0,83	3,48	258	236	18,2	11,3	9,4	12,8	882
D.C.	0,49	3,39	240	161	29,3	9,7	7,2	14,3	822

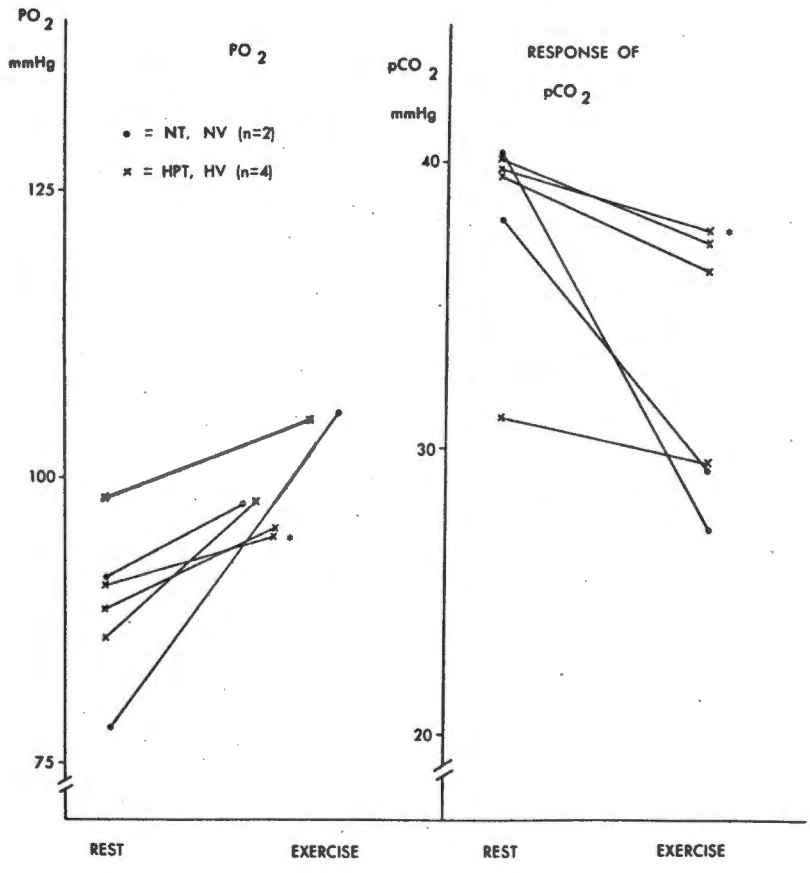

Figure 2 - Response of Respiratory Parameters (pO_2, pCO_2) on Exercise

+ Patient G.D.

It is of interest that the two patients who showed the greatest degree of hyperventilation, assessed on the overall $\dot{V}_E$ and the pCO_2, had the least evidence of overhydration, i.e. the two 'normotensives'. However, the peak exercise pH and pCO_2 fell in all cases as a result of the increased levels of circulating lactic acid. The fall in the pH in all the patients on peak exercise is clearly the result of the outpouring of an organic acid (lactic acid) which the normal blood buffers are unable to neutralize. Although the patients were performing moderate to severe exercise for them, none dropped his pO_2 on exertion, even when the small underestimate of the rolling basal pO_2 is taken into account. Using the sensitive V_D/V_T and $A\text{-}a_o$ indices, only G.D., the most overloaded patient, showed possible evidence of interstitial/alveolar oedema on exercise.

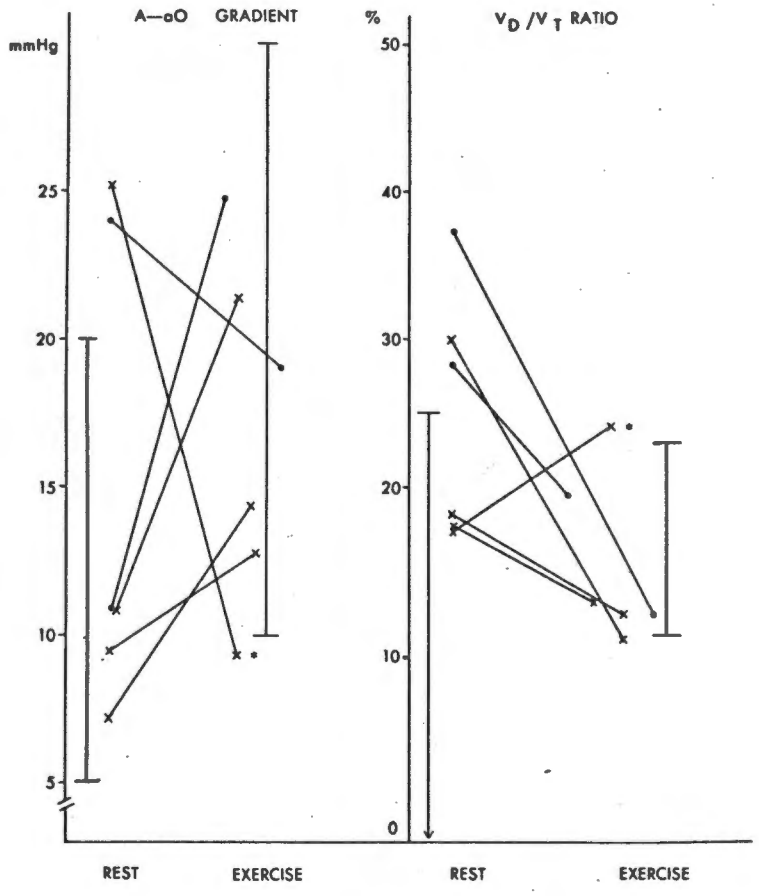

Figure 3 - Response of Respiratory Parameters ($A\text{-}a_o$, V_D/V_T ratio) on exercise
+ Patient G.D.

11.3 Conclusions

The purpose of this chapter is not only to document the changes that may be expected in a healthy group of dialysis patients, but also to show that in spite of subclinical volume overload in the four hypertensives, none with the possible exception of G.D., develop actual heart failure. The lesser hyperkinetic cardiac output response in the volume overloaded patients is thus probably not due to the actual development of heart failure itself, but probably to the increased afterload. The ventilatory response of these 12

patients is largely normal, and any suggestive hyperventilation is probably due to premature lactic acidosis. This latter arises from their overall diminution in effort tolerance, consequent mainly on the underlying anaemia.

CHAPTER 12

EXERCISE RESPONSES IN AN OLDER GROUP OF PATIENTS

12.1 Introduction

Long-term haemodialysis and renal transplantation are complementary forms of treatment and it is clear that some patients are better suited for the one form than the other. There is an increase in the dialysis mortality with increasing age (E.D.T.A., 1975), but the poor results and excessive mortality with transplantation in patients over the age of 50 make long-term dialysis the agreed form of treatment in the older group. Because more and more patients over 40 years are being accepted for long-term dialysis, the haemodynamic responses of this group both at rest and on exercise should be studied.

As previously mentioned, there are well described age related changes in normal subjects in maximal oxygen consumption, heart rate, cardiac output and blood pressure on exercise (Åstrand, 1960; Strandell, 1964; Åstrand and Rodahl, 1970). With increasing age the maximal oxygen consumption, heart rate and cardiac output decline, while the blood pressure and particularly the systolic pressure rises, unless there is concomitant ischaemic heart disease when it may actually fall (Bruce and McDonough, 1969). A similar but less marked decline is seen in the FEV_1 and FVC values, while ventilation and lactic acid production increase. Both the circulatory and ventilatory changes are seen particularly over the age of 30, and in the 61 to 83 year age group the cardiac output is on average 2,0 l/min lower at any level of oxygen consumption.

Julius et al.(1967) compared the blood pressure responses of different age groups and clearly showed that while the resting pressures of an 18 to 34 year old and a 50 to 69 year old group were similar (mean 120/72),the older group reached the same pressure levels (mean 185/92) at half the oxygen consumption ($\dot{V}_{O_2}$ 1,200 ml/min) of the younger group ($\dot{V}_{O_2}$ 2,400 ml/min). This increase in blood pressure was accompanied by a 1,5 l/min decrease in cardiac output at all levels in the older group and a consequent increase in calculated total peripheral resistance. This increase in peripheral resistance is presumably due to age related structural changes in the peripheral vessels.

12.2 Exercise results in a group of older dialysis patients

Although seven patients above the age of 40 were tested, only four are presented, so that the criteria previously laid down in regard to sex, absence of disease, clinical overload, hypertension and no cardiovascular drug therapy are maintained. No control subjects were obtained for direct comparison. All patients were assessed in the same way as the select males.

Tables I and II give the patient data. They were all males and were tested on a day in between their dialysis. Three patients had A-V fistulae while S.D. had a shunt. Their mean age was 48,5 years and they were all big men. The diagnosis was only certain in the two patients who had polycystic disease and their daily urinary output varied between 50 and 300 ml and the serum creatinine between 11,3 and 18 mg/100 ml. E.M. had had lobectomy a year previously and although clinically well, was the only patient not working full-time. Their mean duration on dialysis was 2,2 years and all were on home dialysis. The resting blood pressure, again the mean of three readings, was normal except for

Table I - Patient Data in the Older Group

Patient	Age	Ht.(cms)	Wt.(kg)	BSA	Diagnosis	Duration on Dialysis (years)	Rehabilitation
E.M.	44	174	74	1,88	?	1,75	None
J.A.	49	177	71,4	1,88	Polycystic	3,0	Full
S.D.	50	176	84,5	2,1	Polycystic	2,1	Full
L.M.	51	176	86	2,02	?	2,0	Full
Mean	48,5	176	79	1,99		2,2	
Range	44-51	174-177	71,4-86	1,88-2,1		1,75-3,0	

Table II - Further Patient Data in the Older Group

Patient	BP Rest	H.R. Rest	Overload	Drugs	Hb	C.T.R.
E.M.	140/80	63	0	-	8,4	49
J.A.	121/81	100	0	-	10,2	-
S.D.	161/99	91	±	-	9,6	50
L.M.	135/80	89	0	-	10,3	48
Mean	139/85	86			9,6	49
Range	SBP 121-161				8,4-10,3	48-50
	DBP 80- 99	63-100				

S.D., and their resting heart rate was unremarkable. None of the patients were clinically overloaded, with the possible exception of S.D., and none were on cardiovascular drugs. The mean haemoglobin is higher than in the select group, as is the mean C.T.R. In none of the patients did the fistulae or shunt play a significant haemodynamic role. The autonomic nervous system was tested in all,and the results presented in Chapter 7, Table V under the Older Group apply to these patients.

In Tables III and IV are shown the results of the exercise tests. In general their effort tolerance was not as good as the select males (see Chapter 8), but their efficiency was normal. J.A. who reached the highest $\dot{V}_{O_2}$ (1509 ml/min),was the only patient who became anaerobic which is borne out by his high arterial lactate level at the time. Their ventilation at the fixed points ($\dot{V}_{O_2}$ 0,75 and 1,0) is the same as in the select group. In Table IV it is seen that the heart rate is perhaps slightly lower than the select group, and the predicted maximum oxygen consumption with all its inherent errors is considerably less.

Of greatest interest in extending the argument of this Thesis, is the behaviour of their blood pressure. Their resting levels taken sitting on the bicycle before exercise (134/85) fall in between the resting levels of the 'normotensive' (128/83) and hypertensive 148/97) younger patients. Two patients, J.A. and L.M., have a less hypertensive response on exercise than E.M. and S.D., but when the actual systolic blood pressure levels are plotted out as before with the 'normotensive' and hypertensive regression lines for comparison (Figure 1), the older patients have an even more alarming hypertensive response than the younger group. Because the numbers are so small, no regression equations have been calculated, but visual lines of best fit have been drawn. Nonetheless, it is obvious that the

Table III - Exercise Results in the Older Group

Patient	Final Load (Watts)	Final $\dot{V}_{O_2}$ (ml/min)	Final RQ.	Mechanical Efficiency (ml/min)	$\dot{V}_E$ 0,75	$\dot{V}_E$ 1,0	Lactate (mmole/l)	
							Rest	Peak Ex
E.M.	90	1343	0,975	853	21	30	-	-
J.A.	90	1509	1,039	973	21	30	0,75	6,5
S.D.	60	1257	0,885	1124	24	32	0,94	2,49
L.M.	75	1374	0,963	1080	25	35	0,52	2,88
Mean	79	1371	0,966	1008	22,75	31,75	0,74	3,96
Range	60-90	1257-1509	0,885-1,039	853-1124	21-25	30-35	0,52-0,94	2,49-6,5

Table IV - Further Exercise Results in the Older Group

Patient	H.R 0,75	H.R. 1,0	Pred. $\dot{V}_{O_2}$ Max (ml/min)	BP rest on bike	Final BP	H.R.X SBP X 10^{-2} Rest	$\dot{V}_{O_2}$ 1,0	Final $\dot{V}_{O_2}$ (ml/min)
E.M	98	117	1830	135/75	230/95	88	246	1343
J.A.	121	134	1795	122/84	198/65	121	241	1509
S.D.	125	137	1796	145/100	220/115	147	274	1257
L.M.	105	115	2783	135/80	190/90	120	190	1274
Mean	112	126	2051	134/85	210/91	119	238	1371
Range	98-125	115-137	1795-2783	SBP 122-145 DBP 75-100	SBP 190-230 DBP 65-115	88-147	190-274	1257-1509

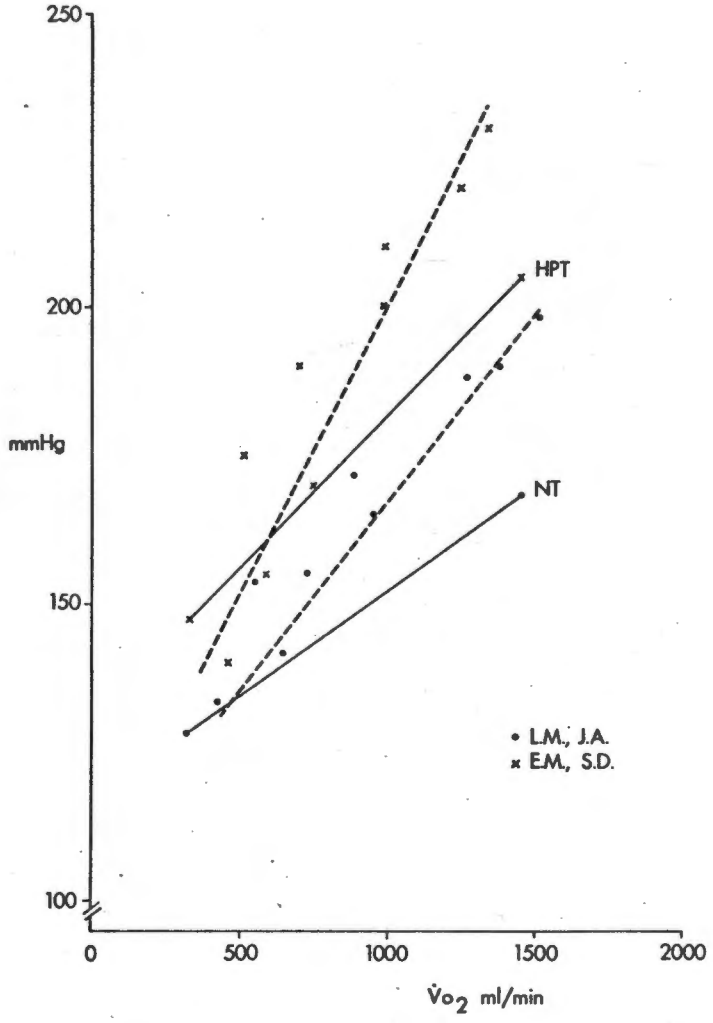

Figure 1 - Systolic Blood Pressure Response of the Older Group Compared to the Younger Subgroups

slopes of these lines are dramatically steeper than in the younger group. Three striking points emerge from this : firstly, the resting pressures in the older patients give no indication of what happens on exercise. Secondly, the older patients also seem to split into two subgroups on exercise, a more hypertensive and a less hypertensive, and finally, the rate of rise of the systolic blood pressure of the more hypertensive subgroup is frightening indeed. In order to emphasize the effect of the combined

tachycardia and systolic hypertension, I have calculated the H.R. SBP product for the older group as a whole at rest and at $\dot{V}_{O_2}$ 1,0. At rest the mean product is 119 but at $\dot{V}_{O_2}$ 1,0 it is 238, and if reference is made to Figure 8 in Chapter 8 this is the level of the six hypertensive select young males. Hence theoretically there is great strain on these patients' hearts in terms of their myocardial oxygen consumption.

Only one of the older group was further investigated to see if the volume/blood pressure hypothesis holds true. Table V shows the patient S.D. who was 50 years old with a haemoglobin of 9,6 gms/100 ml and a C.T.R. of 50 per cent. He developed an alarming hypertensive response on exercise. His total blood volume is below the predicted level (91 per cent), but his total body water is elevated (108 per cent). Clinically, he appeared to have borderline circulatory overload, with a marginally elevated jugular venous pressure at 45^{o}. It is difficult to reconcile the clinical findings with the measured total blood volume : either there was a clinical error, or there was redistribution of the blood volume to his lungs resulting in a high central volume but a normal total volume. Another possible explanation is the known fact that predictions of body volume become more unreliable with increasing age. However, the C.T.R. of 50 per cent, the low-normal P.R.A. values and the expanded total body water plus his resting and exercise hypertension are in favour of circulatory overload.

12.3 Conclusions

The evidence from this older group of patients illustrates that they have decreased work capacity and predicted maximum oxygen consumption compared to the younger group. Their heart rate at certain fixed points may be slower, but there is no difference in their minute ventilation.

Table V - Volume/Blood Pressure Relationship in an Older Patient

Patient	Total Blood Volume			Total Body Water			P.R.A. (ng/ml/hr)		Blood Pressure	
	Measured (litres)	Predicted (litres)	% Predicted	Measured (litres)	Predicted (litres)	% Predicted	Rest	Exercise	Rest	Peak Exercise
S.D.	4,81	5,28	91	47	43,4	108	0,56	0,73	161/99	220/115

What is striking is the frightening rate of rise of systolic blood pressure from perfectly acceptable resting levels, and there may again be two types of response, a more hypertensive and a less hypertensive. The one patient investigated with body volumes and P.R.A. appears to confirm the hypothesis that those with circulatory overload develop the really frightening hypertension. The older patients thus seem to have a disproportionately high peripheral resistance, perhaps related to accelerated vascular disease, and the exercise hypertension and tachycardia may have bearing on their higher cardiovascular mortality compared to an age matched control population.

CHAPTER 13

THEORETICAL CONSIDERATIONS ARISING FROM THESE STUDIES

It is accepted that anaemia, unassociated with renal disease, may produce a hyperkinetic circulation. If the anaemia is severe enough (Hb below 6 to 7 gm/100 ml), the hyperkinetic circulation will be seen at rest, but with lesser degrees of anaemia,exercise or some other form of stress is required to expose the underlying high output state. Both heart rate and stroke volume contribute towards the elevated cardiac output, but the precise mechanisms, whether hormonal or nervous, are not known. Anaemia per se is not associated with hypertension either at rest or on exercise, and in younger patients there is an increased pulse pressure with an actual fall of the diastolic pressure during exercise. Some authors have suggested that mild degrees of anaemia may protect the subject against ischaemic heart disease and hypertension (Elwood, 1974). Other than the effects on the total peripheral resistance due to increasing blood viscosity, little is known about the reaction of peripheral vessels when anaemia is corrected.

In chronic renal disease anaemia, due mainly to decreased erythropoeitin production, appears once renal function had declined to about 25 per cent of normal. Most patients progress slowly to end-stage failure and usually live with their anaemia for a number of years before they are placed on haemodialysis. However, in addition to the burden imposed by their anaemia, other haemodynamic problems appear related to salt and water retention and disturbances of the renin-angiotensin system. There is also impaired

carbohydrate and lipid metabolism, possible metastatic calcification and disturbance of the autonomic nervous system, and once on dialysis, possible haemodynamic burdens from their arteriovenous communication. It is thus not surprising that there is no holistic view of the genesis of the hypertension that is so common in these patients. I will add to the confusion by suggesting that anaemia itself may contribute towards its pathogenesis.

The 12 male patients that I have studied at rest and on exercise belong with few exceptions, to the group whose blood pressure is volume dependent. I feel that their renin-angiotensin system is operating reasonably appropriately to their volume status, although some may argue that in the overloaded patients their plasma renin levels should be depressed even even lower than they are. There is truth in this in that these patients' resting P.R.A. levels (± 0,5 ng/ml/hr taken sitting) are about the same as the mean (0,41 ng/ml/hr taken standing) in the salt loaded controls, whose degree of fluid retention is probably not as great. Nonetheless, the renin-angiotensin system does not appear to be the predominant factor. The standard exercise tests have shown that they develop a striking tachycardia, while some show an accelerating hypertension from previously acceptable levels. Those that develop the hypertensive response are a decade older than those whose response is reasonably normal. The hypertensive response is even more dramatically shown in the four older patients, but the rate of rise in both age groups is clearly disproportionate to either their resting level or to their age. When further investigated, the 'normotensive' patients are normovolaemic and the hypertensive patients hypervolaemic, although clinically not in heart failure. At rest their cardiac output is usually in the normal arange, but on exercise they all show a hyperkinetic circulation, those with the most volume overload being

paradoxically closer to the normal range. Simple 'waterlogging' alone cannot account for the high calculated peripheral resistance, since in P.R., when his body volume returned to normal, the resistance actually became higher and the increased P.R.A. level and blood viscosity do not appear to provide a complete explanation.

How may the known facts of anaemia, volume and age be related to the cardiac output response, the blood pressure and the state of the peripheral vessels ? Increased blood flow, however induced, has been suggested to cause peripheral vasoconstriction, which, if continued, may progress to a more permanent state with elevated blood pressure and a baroreflex mediated decrease in cardiac output. This suggestion is now known as the functional theory of autoregulation and has been propounded chiefly by Borst and Borst-de Geus (1963), Ledingham (1971) and Guyton et al.(1973). Actual proof of this hypothesis is lacking, but there is good evidence that when blood volume is increased, there is an initial rise in cardiac output with a slower rise in blood pressure; the calculated total peripheral resistance gradually increases and finally there is a sustained elevation of the pressure and the resistance, while the cardiac output returns to control levels.

In a patient with anaemia and a hyperkinetic circulation, the peripheral vessels may undergo an initial myogenic vasoconstriction. However, the findings with methoxamine in moderate anaemics (Duke and Abelmann, 1969) and the isovolaemic transfusion of dialysis patients (Kim et al., 1975) where both groups showed a rebound hypertension and elevated peripheral resistance, suggest that there may be more permanent underlying vasoconstriction depending on the duration of the anaemia.

It has been known for many years that hypertension is associated with structural change in the peripheral vessels of many organs. However, this was considered mainly a consequence of hypertension. More recently it has been suggested (Conway, 1963; Folkow, 1971) that the structural change may be involved pathogenetically, and serve at least to perpetuate and aggravate the hypertension. This theory is now called structural autoregulation. It is not too difficult to imagine that functional autoregulation may progress, if maintained for long enough, to actual structural change. This progression has in fact been shown to occur in rats within three to six weeks (Lundgren, 1974; Weiss, 1974). Conversely, depending on the duration of the structural change, removal of the precipitating factor or control of the blood pressure will result in slow reversal of the vascular damage.

I suggest in renal patients, who have had some degree of anaemia for a number of years and who develop a hyperkinetic circulation at least on mild everyday exertion, that functional autoregulation leads in time to more permanent structural change. This situation is aggravated by cyclical salt and water retention and angiotensin II induced vasoconstriction once they are on haemodialysis. If the patient is markedly anaemic (Hb less than 5 gm/100 ml), then severe tissue anoxia with vasodilatation may mask the underlying vascular thickening, and hypertension at rest or on exercise may not be obvious, even with circulatory volume overload. With lesser degrees of anaemia (Hb 5 to 10 gm/100 ml) the thickened vessels interact with volume overload, prevent the expected exercise vasodilatation and accelerating hypertension emerges. Paradoxically, the combined effect of volume overload and increased resistance then depresses the anticipated hyperkinetic circulation, but this is at the expense of a high peripheral

resistance and hypertension. The reason why their blood pressure appears relatively normal at rest but accelerates on exercise is explained by the Poiseuille equation which states that flow through a tube varies directly with the fourth power of the radius (r^4) or that the pressure drop across the vessel varies directly with the flow and inversely with r^4. Hence on exercise where the anticipated vasodilatation is prevented by the increased wall/lumen ratio, hypertension becomes more marked.

Age is clearly important in determining the elasticity of the peripheral vessels. With increasing age a normal subject is more prone to vascular structural change. The addition of the normal age related changes to the changes postulated above, plus any changes induced by abnormal carbohydrate, lipid and calcium metabolism, is more than sufficient to explain the accelerated atherosclerosis seen in dialysis patients.

Although this postulate bodes ill for the dialysis patient, there are also encouraging aspects. It has been shown (Lundgren, 1974; Weiss, 1974) in the rat that, depending on the duration of the vascular changes, control of hypertension may lead to slow resolution of these changes. The pathological nature of these changes is unknown, but may be related to collagen and elastic invasion of the walls of the resistance vessels, which reduce their wall/lumen ratio. Rigid control of the rats' blood pressure leads not only to a reduction of wall/lumen ratio but also to a decrease in left ventricular hypertrophy. Thus, sustained and meticulous control of the hypertension in dialysis patients may reduce the elevated peripheral resistance and possibly the cardiovascular mortality. The therapeutic implications and choice of drugs will be discussed in more detail in the last chapter.

CHAPTER 14

PRACTICAL CONSIDERATIONS ARISING FROM THESE STUDIES

14.1 Introduction

In the first part of this chapter an attempt will be made to lend statistical respectability to some of the variables, such as anaemia, blood pressure and age, that have been found to influence the patients' exercise performance. I hope that the statistical analysis will also place some of these variables in greater perspective. Other practical aspects such as the importance of nutrition will be stressed as well.

Some objective measurement of exercise performance must be established with which to correlate the above variables. Although submaximal tests provide a reasonably objective assessment of exercise performance, the most objective test is the subject's maximal oxygen consumption. However, because of the potential risk to the chronically ill of maximal testing, the heart rate measured during submaximal exercise at a fixed oxygen consumption has been chosen as the simplest and most reliable yardstick of physical performance. All variables will therefore be correlated with the heart rate at an oxygen consumption of 1/min ($H.R._{1,0}$). For these correlations the results of the 12 select young males have been used, initially as a whole and later divided into 'normotensive' and hypertensive subgroups. The correlations have all been made by single regression analysis using a Sumlock Compucorp 344 Microstatistician and standard statistical methods.

14.2 Correlations in the select group as a whole (12 patients)

14.2.1 Correlation of age with $H.R._{1,0}$

Increasing age is associated with a progressive slowing of the exercise heart rate, but this slowing is only clearly seen on maximal testing and over a fairly wide age range. Nonetheless, in the select group age correlated negatively with $H.R._{1,0}$ ($r = -0,83$, $p < 0,001$), showing that even though the age range was only 20 years (19 to 39) the older patients had a lesser exercise tachycardia. When the age factor was looked at in the matched control group (12 males, age 19 to 37 years), there was actually a positive correlation ($r = 0,61$, $p < 0,05$). A number of excellent studies (Åstrand, 1960; Strandell, 1964) have clearly established the decrease in maximal heart rate with increasing age over many decades and must be accepted. Thus the positive correlation in the control group must be due to the relatively small age range and the absence of maximal heart rates, but the striking negative correlation in the patient group suggests that age or some aspect of the aging process assumes disproportionate influence.

14.2.2 Correlation of peak systolic blood pressure with $H.R._{1,0}$

Structural vascular change is the most obvious factor accompanying increasing age and this would be expressed as a high peripheral resistance or an elevated blood pressure. Peak systolic pressure (peak SBP) gave a a negative correlation ($r = -0,64$, $p < 0,05$), showing that increasing hypertension on exercise was associated with a slower heart rate, which confirms the impression that the baroreceptors are acting reasonably normally. Thus it may be that accelerated vascular damage is the factor which gives the age correlation such importance in this group.

14.2.3 Correlation of haemoglobin with $H.R._{1,0}$

Much argument has been devoted to the importance of the underlying anaemia in producing the hyperkinetic circulation seen on exercise. When haemoglobin alone is weighted, the negative correlation ($r = -0,54$, $p = 0,1 - 0,05$) is not nearly as impressive as expected. However, perhaps anaemia and the blood pressure are interacting. In order to assess this the two subgroups must be considered separately.

14.3 Correlations in the 'normotensive' subgroup (six patients)

14.3.1 Correlation of peak SBP and Hb with $H.R._{1,0}$

When the SBP is considered, there is no correlation with the exercise heart rate ($r = 0,41$, P = N.S.), while with the Hb alone there is a much stronger correlation ($r = -0,69$, $p = 0,2 - 0,1$), but this does not reach statistical significance, probably because of the small numbers.

14.4 Correlations in the hypertensive subgroup (six patients)

14.4.1 Correlation of peak SBP and Hb with $H.R._{1,0}$

In this group the exact opposite is found : peak SBP almost reaches statistical significance in spite of the small numbers ($r = -0,73$, $p = 0,1$), while the anemia is of no importance ($r = -0,3$, p = N.S.).

No multiple regression analysis was performed because the numbers, particularly in the subgroups, are too small, but the single analysis confirms the clinical impression that increasing age and increasing hypertension have a negative effect on the exercise heart rate. When these are absent, as in the younger 'normotensive' patient, the exercise

heart rate is largely determined by the degree of underlying anaemia : the more anaemic, the greater the exercise tachycardia.

14.5 Other correlations with $H.R._{1,0}$ in the select group as a whole

A weak negative correlation was found with duration on dialysis. This is difficult to interpret because those longest on dialysis tended to be older and also showed the most hypertensive response. There was no correlation with the original disease or the existing residual renal function, measured by the plasma creatinine and the 24 hour urinary volume. However, there was a suggestive negative correlation with body weight ($r = -0,64$, $p < 0,05$) indicating that those with smaller muscle bulk had greater exercise tachycardia. The correlation in the control males ($r = -0,41$, $p = 0,2 - 0,1$) was not as strong as in the dialysis patients, but it was clear that the lighter individuals could do less than their heavier colleagues.

The strong correlation in the patients between weight and physical performance raises the question of their nutritional status. When their observed weight was compared to a predicted ideal weight based on the formula for males that predicted weight = 0,79 (height in cms) - 60,7, most were found to be below their ideal weight. These figures are shown together with their total protein and serum albumen levels on the lefthand side of Table I. Although the predictions are for an American population and are not necessarily valid across the Atlantic, the select group as a whole appears to be below their ideal weight and when only the 'normotensive', normovolaemic subgroup is considered, this is more striking. This suggestion of undernutrition is not borne out by the total protein and serum albumen levels, which, with the exception of G.F. (albumen 2,6 gm/100 ml), are normal.

Table I - Nutrition, Lipids and Calcium Metabolism in the Select Group

Patient	Observed Wt(kg)	Predicted Wt(kg)	Relative Wt (%)	Total Protein (gm/100 ml)	Serum Albumen (gm/100ml)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Calcium (mg/100ml)	Phosphorus (mg/100 ml)	CaX PO_4
1. 'Normotensives'										
R.B.	60,3	75,2	80	7,7	4,7	-	-	10,9	3,9	43
K.E.	65,5	76,4	87	7,7	5,0	138	165	10,5	3,9	41
A.P.	85,9	83,1	103	-	-	150	-	9,9	3,7	37
B.B.	57,0	78,3	73	7,6	4,7	160	115	10,9	5,1	56
M.B.	79,5	81,5	98	7,2	4,7	-	-	11,5	5,5	63
G.F.	57,4	67,7	85	6,6	2,6	205	-	10,6	3,6	38
2. Hypertensives										
G.D.	87,5	76,8	114	7,9	4,2	215	190	9,9	5,5	55
P.R.	73,0	76,8	95	-	-	170	185	9,6	5,1	49
D.P.	63,7	74	86	7,4	5,0	-	-	12,3	4,9	60
H.D.	65,2	68,9	95	7,4	4,3	-	-	9,7	4,3	42
A.D.	72	74	97	-	-	180	-	11,1	4,8	53
D.C.	82,7	79,5	104	7,1	4,2	210	180	10,9	3,7	40
Mean	71	76	93	7,4	4,4	179	167	10,7	4,5	48

Most of the patients claimed to be eating the recommended 1 gm of protein / kg body weight/day, but this may not be sufficient for optimal muscle bulk and hence physical fitness.

14.6 Prognostic implications of these findings

In most reviews of the causes of dialysis deaths, cardiovascular disease accounts for the greatest number. This is not a universal finding and in particular was not the experience at Charing Cross Hospital. The reason for this lack of agreement may be that patients have not been on dialysis long enough, and that as dialysis survival extends beyond 10 years and as the mean age shifts into the fifth and sixth decades, the pattern of cardiovascular related deaths will become clearer. In earlier years much emphasis was placed on the role of hypertension and fluid overload as a cause of these cardiovascular deaths, but until recently (Lazarus et al., 1974 and 1975; Hull et al., 1975) there has been a certain complacency about blood pressure control and the emphasis has shifted to the role of carbohydrate intolerance, lipid abnormalities and metastatic calcification.

The righthand side of Table I illustrates the lipid status in some of the patients at the time of testing, as well as the serum calcium and phosphorus, and the calculated calcium/phosphorus product. Although the plasma cholesterol and triglyceride were not taken in the fasting state, the levels shown are reasonably normal for 19 to 39 year old males and are certainly not indicative of severe hyperlipoproteinaemia. In all cases the serum phosphorus was well controlled and most patients were not routinely taking aluminium hydroxide. Only one patient, A.D., was known to have severe hyperparathyroidism, and no patients had gross

metastatic calcification. This is endorsed by the calcium/phosphorus product which was always below 70 with a mean of 48. Conversely, in terms of muscle fatigue, none showed obvious phosphate depletion and, although no balance studies were performed, this is unlikely to be responsible for the poor work capacity.

We thus return to what I consider are the most important risk factors, namely uncontrolled hypertension and tachycardia. As shown the pressure levels were acceptable at rest and the heart rates, although elevated, were not particularly striking. However, on mild everyday activity tachycardia and in some cases alarming systolic hypertension developed. It may be argued that patients deliberately limit their expenditure of effort during daily activity, and so reduce the ill effects of their high heart rate systolic blood pressure product. This argument would be very difficult to refute without continuous heart rate and blood pressure monitoring, comparing the dialysis patients to controls matched for daily activity. This was not done. However, as the study stands, the combination of even the mild resting hypertension and tachycardia will impose a strain on their hearts, and this can only become worse on exercise.

14.7 Therapeutic implications

Long-term haemodialysis is becoming the treatment of choice for the older patients, but there are, in all integrated programmes, a considerable number of younger patients who for various reasons are not transplanted. It is accepted that other metabolic disturbances contribute towards the accelerated atherosclerosis and require attention, but I would like to focus on blood pressure control and anaemia.

Doctors should become more aware of the hazards of mild uncontrolled hypertension and the patients should be viewed in exactly the same light as any other hypertensive. In the first instance the blood pressure should arbitrarily be kept below $\frac{140}{90}$ at all times including on the day of dialysis. Patients on home dialysis who are well and are only seen intermittently, should be encouraged to keep accurate daily checks on their blood pressure and the hazards of mild uncontrolled hypertension explained to them.

How the blood pressure is controlled will depend on the underlying cause. In the majority of patients gradual body volume depletion will reduce the levels. This would mean initially an increase in the symptoms of postdialysis lassitude, headache and dizziness, but it is a small price to pay in order to prevent the inevitable consequences of uncontrolled hypertension. When volume overload is clinically obvious the therapeutic approach is straightforward, but exercise testing either on a bicycle or more simply with a step test or possibly even with some form of static handgrip test, will indicate those young patients with subclinical overload. In assessing the older patients data on age matched controls must be available, as both the normovolaemic and hypervolaemic patients develop variable hypertension on exercise. If simple weight reduction is not accompanied by a fall in blood pressure, at least two body volume compartments should be measured together with the plasma renin activity in order to indicate those patients in whom the renin-angiotensin system is playing only a contributory or the dominant role. In these, an early decision on whether to institute drug therapy or to perform bilateral nephrectomy should be made. Bilateral nephrectomy will not be discussed further, but if adequate control with drugs and fluid depletion is not

achieved, this must be done without undue procrastination, albeit as a last resort.

What antihypertensive therapy to recommend is difficult. One must balance the problems posed by the high peripheral resistance against those due to the compensatory hyperkinetic circulation. Drugs such as alpha methyl dopa, minoxidil and diazoxide cause fluid retention but this may be controlled by dialysis. The vasodilator, hydralazine, alone may increase the tachycardia, whereas beta blockade alone would at least increase their fatiguability and might precipitate frank heart failure. However, a combination of hydralazine, minoxidil or diazoxide and a beta blocker would theoretically act to control both the hypertension and the tachycardia. Whatever drug regimen is used, a certain price will be paid in side effects, but the overriding point is to control the blood pressure so that the underlying structural vascular change is given a chance to resolve.

The final therapeutic implication is to focus more closely on the anaemia. Much research is currently in progress to reduce dialyser blood loss and to give adequate replacement of iron, vitamins and amino acids. More to the point is the stimulation of the remaining erythropoeitin and for the future the use of synthetic erythropoeitin itself. Once such a breakthrough is made, it should not be reserved only for patients actually on dialysis, but should also be used as part of the conservative management of chronic renal failure as soon as anaemia becomes apparent.

14.8 Exercise testing and long-term care

In addition to providing an investigative and diagnostic tool, standardized submaximal exercise testing has other applications. Because of its reproducibility and because it stresses the patient as a whole, it could provide a better index of progress than any other single measure, e.g. haemoglobin or the electromyograph. Not only could it provide a yardstick of physical rehabilitation, but it could also be used as an index for comparing various dialysis regimens. Thus in a simplified form exercise testing should become routine in the assessment of all dialysis patients since it measures 'the capacity of the whole organism, not just the heart' (Merrill, 1975).

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